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Nanomaterials augmented bioeffects of ultrasound in cancer immunotherapy

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ABSTRACT

Immunotherapy as a milestone in cancer treatment has made great strides in the past decade, but it is still limited by low immune response rates and immune-related adverse events. Utilizing bioeffects of ultrasound to enhance tumor immunotherapy has attracted more and more attention, including sonothermal, sonomechanical, sonodynamic and sonopiezoelectric immunotherapy. Moreover, the emergence of nanomaterials has further improved the efficacy of ultrasound mediated immunotherapy. However, most of the summaries in this field are about a single aspect of the biological effects of ultrasound, which is not comprehensive and complete currently. This review proposes the recent progress of nanomaterials augmented bioeffects of ultrasound in cancer immunotherapy. The concept of immunotherapy and the application of bioeffects of ultrasound in cancer immunotherapy are initially introduced. Then, according to different bioeffects of ultrasound, the representative paradigms of nanomaterial augmented sono-immunotherapy are described, and their mechanisms are discussed. Finally, the challenges and application prospects of nanomaterial augmented ultrasound mediated cancer immunotherapy are discussed in depth, hoping to pave the way for cancer immunotherapy and promote the clinical translation of ultrasound mediated cancer immunotherapy through the reasonable combination of nanomaterials augmented ultrasonic bioeffects.

1. Introduction

Cancer remains a major medical problem worldwide and is the leading cause of human death. Traditional treatments include surgery, chemotherapy and radiotherapy. However, the pathological process of cancer is complex, which may involve changes of the external and internal microenvironment of pathological cells, gene expression and destruction of the endocrine system, *etc*. [1–3], especially in the stage of metastasis, leading to the limited effectiveness.

Immunotherapy, as a turning point in cancer treatment, with the development of immunotherapies such as immune checkpoint blockades (ICB) and chimeric antigen receptor T-cell immunotherapy (CAR-T cell immunotherapy), provides an effective strategy for eliminating refractory pathological cells at both primary and distal tumors, by boosting the body's immune system in the last decade [4–6]. Meanwhile, the memory T cell responses induced by immunotherapy can prevent tumor recurrence effectively. Therefore, immunotherapy is becoming a mainstream strategy in cancer treatment. Although immunotherapy is experiencing an unprecedented boom, it still confronted some obstacles, which limited the widespread use of immunotherapy. For instance, ICB therapy benefits less than 13 % of cancer patients [7, 8], the response rate of CAR-T therapy in patients with solid tumors is less than 15 % [9] and there are severe immune related side effects in treatment [10,11], among others. These problems have motivated the development of more adaptive strategies which are used to enhance the benefits of immunotherapy and reduce off-target toxicity.

At this point, the combination of therapies comes into play. Among them, ultrasound has attracted wide attention due to its advantages of non-invasiveness, security, deep tissue penetration, fewer side effects and so on. By adjusting the power and intensity of ultrasound, a variety of biological and physical effects, including thermal and non-thermal effects [12], can be induced for immunotherapy. The thermal effect is the result of sound energy being absorbed and converted into mechanical compression and thermal energy as ultrasound propagate through

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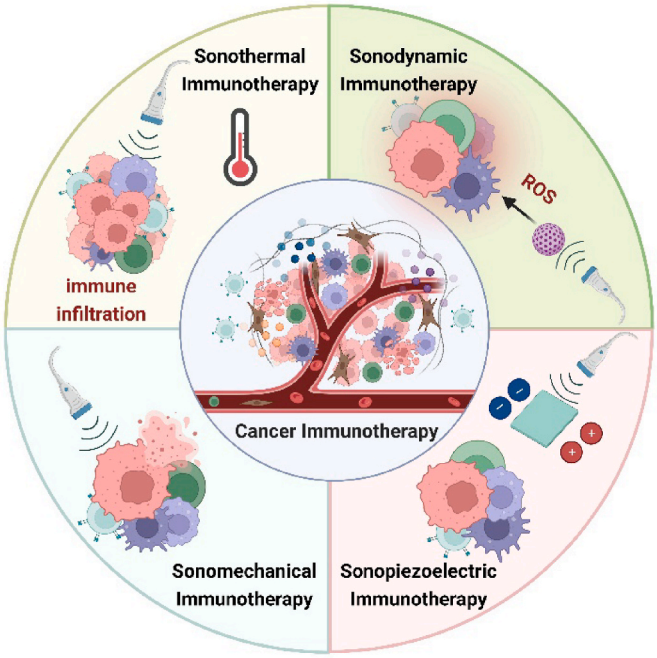

Fig. 1. Schematic illustration of nanomaterials augmented ultrasonic bioeffects in cancer immunotherapy. Created with BioRender.com.

tissue. Excessive heat generated by local ultrasound irradiation can destroy proteins and other organelles, induce immunogenic cell death (ICD) while minimizing damage to surrounding tissues. Non-thermal (mechanical) effects include cavitation and acoustic radiation force (ARF) that can cause mechanical effects to function as antitumor immunotherapies. In addition, the cavitation effect leads to pyrolysis and sonoluminescence, trigger sonosensitizer to produce ROS (also known as chemical effects), induce ICD for immunotherapy [13,14]. However, due to the heterogeneity of the tumor and complex immunosuppressive microenvironment, the efficacy of immunotherapy is still not perfect even when combined with ultrasound.

With the rapid development of molecular engineering and synthetic biology, various nanomaterials have been used to construct ultrasound responsive nanoplatforms, which improve the bioeffects of ultrasound, promote the progress of ultrasound mediated immunotherapy and achieve high therapeutic efficacy [15–18]. These nanoplatforms not only modulate the tumor immunosuppressive microenvironment and restore immune surveillance, but also utilize the biological effects of ultrasound to further enhance antitumor efficacy, not only for the primary tumor, but also for metastatic and recurrent tumors [19]. In a word, the boom of nanomaterials has injected new vitality into ultrasound mediated antitumor immunotherapy.

In this review, we first gave a brief introduction to cancer immunotherapy, followed by a comprehensive summary of the recent progress and latest situation in nanomaterials-augmented sonotherapies in cancer immunotherapy, including sonothermal immunotherapy (iSTT), sonomechanical immunotherapy (iSMT), sonodynamic immunotherapy (iSDT) and sonopiezoelectric immunotherapy (iSPT). We systematically summarized representative sonotherapies in cancer immunotherapy, from the design of nanoplatforms to their different principles and mechanisms involved in antitumor immunotherapy. At the end of this review, we also discussed the faced challenges in this field and prospects for clinical translational applications of these sonotherapies in cancer immunotherapy (Fig. 1). It is hoped that this review can provide guidance for the application of ultrasound bioeffects mediated immunotherapy, open a new era of cancer therapy, and ultimately achieve clinical translation to bring good news to patients.

2. Cancer immunotherapy

Immunotherapy, which aims to eliminate tumor cells by unleashing the host immune system rather than directly killing them, is a monumental breakthrough in cancer treatment that has revolutionized cancer treatment protocols [20]. The innate and adaptive immune systems, including T cells, dendritic cells (DCs), macrophages, natural killer (NK) cells and B cells, contribute to tumor progression and immune response [21–23]. Effective immune response can alter tumor phenotype and impair cell function, and even eradicate tumor cells, which is not only effective against primary and distant tumors, but also effectively prevents tumor recurrence through immune memory effects [24]. As a result, immunotherapy has attracted a lot of attentions from researchers and oncologists, injecting new energy into cancer therapeutics.

2.1. Mechanism of cancer immunotherapy

Immune cells are the cornerstone of immunotherapy, so understanding the infiltration of immune cells in the tumor microenvironment (TME) is a key factor in deciphering the mechanisms of immunotherapies, improving immune response and developing new strategies for cancer immunotherapy. Immune cells infiltrate tumors through innate and adaptive immune systems and play a crucial role in tumor initiation and progression. Innate immune cells, including NK cells, macrophages, DCs, *etc*., exert antitumor effects by directly killing tumor cells or triggering adaptive immune responses [25–27]. The adaptive immune system is dominated by lymphocytes, including B cells and T cells, where B cells are involved in humoral immune responses and T cells are involved in cell-mediated immune responses [28–32].

At present, cancer immunotherapy is mainly mediated by T cells and depends on the trigger efficiency of the cancer immunity cycle. In brief, dying tumor cells such as apoptotic or necrotic cells release tumor-associated antigens (TAAs) and costimulatory signals. Antigen-presenting cells (APC) capture TAAs and degrade them into peptides. At the same time, under the action of costimulatory molecules, APCs developed and matured. Subsequently, mature APCs migrate to draining lymph nodes (DLNs), where complex peptides are presented to native T cells, activating cytotoxic T lymphocytes (CTLs). These CTLs proliferate through cloning, enter the bloodstream, infiltrate tumor tissues, and specifically recognize and kill tumor cells by releasing toxic molecules. The dying tumor cells then release TAAs and costimulatory signals to start the next cycle [33,34]. In this way, long lasting antitumor effects can be achieved [35].

2.2. Categories and characteristics of cancer immunotherapy

Although the immune system can prevent or slow the growth of cancer, cancer cells can achieve immune escape by interfering with the immune system's response to cancer cells through genetic mutations, surface checkpoint proteins, or altering normal cells surrounding the tumors. Immunotherapies, including immune checkpoint blockers, T-cell transfer therapy, monoclonal antibodies, cancer treatment vaccines, oncolytic virus therapy, cytokines and immune system modulators, help the immune system to act better against cancer.

2.2.1. ICB

Immune checkpoints are an important part of the immune system, acting as a "brake" system when the immune system attacks invaders such as bacteria and viruses, preventing the immune system from attacking normal cells. Immune checkpoints come into play when immune checkpoint proteins on the surface of T cells recognized and bind to partner proteins on the tumor cells [36]. When checkpoints bind to partner proteins, they send an "off" signal to T cells for stealth purposes and prevents the immune system from killing cancer cells. Immune checkpoint inhibitors (ICIs) are drugs that unlock "brake" system, blocking the "off" signal by preventing the immune checkpoint protein

from binding to its partner protein, allowing T cells to kill cancer cells [37]. ICBs approved for clinical use by Food and Drug Administration (FDA) block programmed cell death protein 1 (PD-1), programmed death ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), which allow cells to continue to grow after they become cancerous [38,39].

2.2.2. T-cell transfer therapy

T-cell transfer therapy is a type of synergistic therapy that enhance immune cells to attack cancer, is also called adoptive cell therapy, adoptive immunotherapy, and immune cell therapy [40]. It consists of CAR-T, tumor-infiltrating lymphocyte (TIL) therapy and engineered T cell receptor (TCR) therapy [41,42]. They collect immune cells from tissues around tumors, cultivate them in the lab, to produce a large number of immune cells, which are then injected them back through veins to find and kill more cancer cells.

2.2.2.1. CAR-T therapy. CAR-T therapy is a treatment that increases the ability of T cells to kill cancer cells by adding a gene for special receptors called chimeric antigen receptors (CARs) to the surface of T cells so that they can bind to special proteins on the surface of cancer cells [43]. As of now, only few CAR-T drugs, such as Kymriah and Yescarta, have been approved by the FDA for acute lymphoblastic leukemia and large B-cell lymphoma [44], so researchers are working to find new ways for utilizing CAR-T to treat cancer. One way is to take cells from healthy donors and make ready-to-go treatments for patients with cancer [45].

2.2.2.2. TIL therapy. Lymphocytes within or surrounding tumors, called TILs, have the ability to recognize tumor cells, but TILs are not enough to kill cancer cells or overcome the immune system suppression signals [46]. So, researchers took T cells out, cultured them in the lab to generate large amounts of T cells, which were then transfused back into the body, producing powerful antitumor abilities. At present, although researchers have made some progress, there is still some distance from clinical translation [47–49].

2.2.2.3. Engineered T-cell receptor (TCR) therapy. TCR therapy removes T cells from blood and reprograms them in the lab. The engineered T cells are able to find tiny targets on the surface of cancer cells and bind them to exert better antitumor effects [50]. Currently, FDA has not approved any TCR therapies, and studies remain in preclinical trials in patients with certain types of sarcoma and advanced melanoma [51,52].

2.2.3. Monoclonal antibodies

Antibodies are proteins produced by the immune system. As they circulate through the body, they can bind to specific proteins on cancer cells, called antigens, and then mobilize the immune system to destroy the antigen-containing cancer cells. In other words, it is both targeted therapy, which can target and bind to cancer cells, and immunotherapy, which enables the immune system to better find and attack cancer cells [53]. Researchers can design antibodies that target certain antigens on cancer cells and make many copies of antibodies in the lab, called monoclonal antibodies (mAbs). However, finding the right antigens for various types of cancer is not so easy. So far, monoclonal antibodies have been shown to be more effective against some cancer types than others. At present, monoclonal antibodies used for cancer treatment mainly include naked monoclonal antibodies, conjugated monoclonal antibodies and bispecific monoclonal antibodies.

2.2.3.1. Naked monoclonal antibodies. Naked monoclonal antibodies, which have no drugs or radioactive substances attached, are the most commonly used type among monoclonal antibodies. They work by boosting the immune system's response to cancer, or by attaching to and blocking antigens on cancer cells that help cancer cells grow or spread. For instance, HER-2 is highly expressed on the surface of breast cancer and gastric cancer cells, and when it is activated, it promotes the growth of cancer cells. Trastuzumab is an antibody that targets the HER-2 protein, and when it binds to HER-2, it stops the growth of cancer cells [54].

2.2.3.2. Conjugated monoclonal antibodies. Conjugated monoclonal antibodies are homing antibodies that bind to chemotherapy drugs or radioactive particles and deliver the conjugated substances to cancer cells [55,56]. They deliver drugs or radioactive particles to where they are most needed, reducing damage to normal cells and tissues. Brentuximab vedotin, for example, both targets an antibody to CD30 and simultaneously attaches to a drug called MMAE [57,58]. Ibritumomab tiuxetan is an antibody that targets the CD20 antigen and delivers radioactive Yttrium-90 to cancer cells [59,60].

2.2.3.3. Bispecific monoclonal antibodies. Bispecific monoclonal antibodies can pair two proteins at the same time, pulling the distance between T cells and cancer cells, and improving the ability of the immune system to kill cancer cells [61]. For example, blinatumomab, while binding to CD19, which is highly expressed in leukemia and lymphoma cells, can also bind to CD3, which is highly expressed in T cells, promoting T cells to be infinitely close to tumor cells and exerting tumor-killing effects [62,63].

2.2.4. Cancer treatment vaccines

Cancer treatment vaccines, which treat cancer by identifying TAAs in an attempt to boost the immune system's natural defenses against cancer cells, unlike cancer prevention vaccines against the HPV virus, they were developed for cancers that have already occurred. Cancer treatment vaccines are usually composed of cancer cells, parts of cells or pure antigens, which are usually combined with substances called immune adjuvants to further enhance the antitumor immune response. In addition, the immune system has special memory cells that can continue to function long after vaccination, preventing the recurrence of tumors. Currently, FDA has approved two treatment vaccines, Sipuleucel-T (Provenge) for advanced prostate cancer that has not responded to endocrine therapy [64], Talimogene laherparepvec (T-VEC) for advanced melanoma and *Bacillus* in which T-VEC is based on herpes simplex virus type 1, also known as oncolytic virus therapy [65,66].

2.2.5. Oncolytic virus therapy

Oncolytic virus therapy is a new generation therapy after ICIs and CAR-T therapy for malignant tumors. The idea of this therapy is to selectively infect tumor cells with natural or genetically recombinant viruses, replicate them in large quantities, kill tumor cells by lysing tumor cells directly. The progeny virus particles released after cell lysis continue to infect neighboring tumor cells. After the viruses enter the body, they will trigger the clearance of the immune system and induce the infiltration of lymphocytes and APCs. At the same time, TAAs released by tumor cells recruit immune cells such as DCs to enter the tumor and activate the local antitumor immune response, thereby generating a specific immune response against tumor antigens and ultimately forming a long-lasting antitumor immune response to prevent tumor recurrence and metastasis [67]. Studies have shown that oncolytic viruses can improve overall survival in different types of tumors and at different stages of progression, even in metastatic and incurable tumors. For patients with advanced tumors, oncolytic virus therapy is considered to be one of the most important means to save lives, and can even achieve complete regression or remission [65,66,68].

2.2.6. Cytokines

Cytokines are small proteins that are crucial for immune response and inflammation. Cytokines are released, to send signals to the immune system, causing tumor cells to die, supporting the growth and activity of normal cells, thereby enhancing antitumor activity. Chemokines are

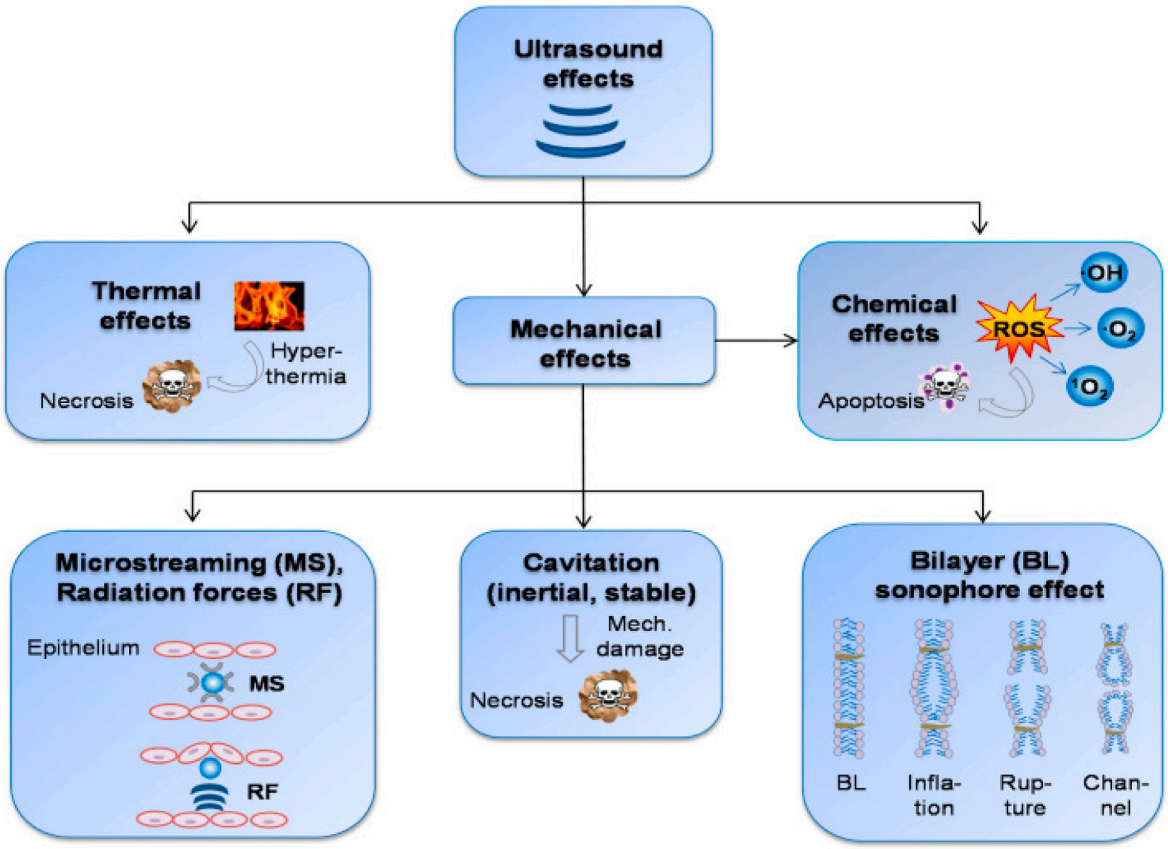

Fig. 2. Schematic diagram of biological effects of ultrasound. Reprinted with permission from Ref. [85]. Copyright 2021, MDPI.

special types of cytokines that include interleukin (IL), interferon (IFN), tumor necrosis factor (TNF), and growth factor [69]. Some of these cytokines can be reprogrammed in the lab to treat cancer while prevent or mitigate the side effects of chemotherapy. The most common ones are interleukins (ILs) and interferons (IFNs).

2.2.6.1. ILs. ILs are proteins produced by white blood cells and act as signals between these cells, also known as T cell growth factors. There are several types of interleukins, including IL-2, which helps immune system cells grow and differentiate faster, increases the number of killer T cells and NK cells, and triggers an immune response against cancer [70]. Synthetic IL-2 is approved to treat advanced kidney cancer and metastatic melanoma. It can be used alone or in combination with chemotherapy or other cytokines such as IFN-α.

2.2.6.2. IFNs. IFNs are chemicals that fight viral infections or cancers, including IFN-α, IFN-β, and IFN-γ. Of these, only IFN-α is used to treat cancers, which enhances the ability of NK cells and DCs to attack cancer cells, and also slow down the growth of cancer cells by directly destroying the blood vessels [71]. IFN-α can be used to treat hairy cell leukemia, chronic myelogenous leukemia, cutaneous T-cell lymphoma, kidney cancer, Kaposi sarcoma, *etc.* [72].

2.2.7. Immune system modulators

Immunomodulators directly act in the immune system by increasing or decreasing the expression levels of certain proteins, enhancing the activity of the immune system and better fighting against cancers. They include thalidomine, lenalidominde, pomalidomide and imiquimod, in which thalidomine, lenalidominde and pomalidomide can prompt cells to release IL-2, exerting antitumor effects [73], imiquimod is applied to the skin as a cream that stimulates local immune responses against melanoma [74].

2.3. Limitations of immunotherapy

Despite tremendous progress in immunotherapy, its clinical translation still faces many challenges. For example, due to the different content of gene mutations in different tumor cells, the expression of tumor neoantigens and MHC proteins are different, and the subset of patients with weak antigenicity and MHC downregulation will have a low immune response efficiency. In addition, some immunotherapy targets are also distributed on normal organs, which inevitably brings some adverse events that require treatment discontinuation, such as blocking PD-1/PD-L1 or CTLA-4 pathway will cause some autoimmune diseases. But the challenges are not limited to these two aspects [10,75]. For T cell transfer therapy, although it has gained a foot hold in epithelial tumors and hematological cancers, it is still a problem to be solved to improve the efficacy due to immune editing and the inherent escape mechanism of cancers [76,77]. In addition, CAR-T therapy causes cytokines release syndrome, while TILs cause capillary leak syndrome, which limits their further application [78]. Over the past few decades, the identification of tumor antigens has enabled the design of vaccines, and tremendous efforts have been made to develop them, but very few therapeutic cancer vaccines have been approved. This is mainly due to the poor immunogenicity of the antigens contained in the vaccine and the presence of immunosuppressive factors in the TME. In addition, tumor vaccines can cause flu-like symptoms, tumor lysis syndrome, severe allergic reaction, and even stroke [79,80]. Due to these challenges, there is an urgent need to develop safer and more effective immunotherapeutic strategies.

3. Principles of ultrasound in cancer treatment

Ultrasound is a periodic vibrational mechanical wave with frequency exceeding the upper hearing limit of the human ear (20 kHz). It is widely

used in clinical diagnosis because of its simplicity, non-invasiveness and absence of ionizing radiation [81,82]. Due to the real-time image navigation, precise spatiotemporal control, good tissue penetration depth, and fewer side effects of ultrasound-mediated therapy, the biomedical application of ultrasound has expanded to the therapeutic field, especially in the burgeoning field of tumor immunotherapy [83]. The therapeutic effect of ultrasound is realized through different biological effects produced by different intensities and frequencies, which are roughly classified into two categories: low power and intensities, and high power and intensities [84]. At higher frequencies, ultrasonic energy is more easily absorbed and attenuated, thus reducing penetration into deep tissue, and accompanied by the generation of thermal effect. Increasing ultrasonic intensity can control the energy acting on the target site. In addition, ultrasonic irradiation time and pulse duty cycle also affect ultrasonic effect.

Biological effects mediated by ultrasound are usually divided into thermal effects and mechanical effects [85] (Fig. 2). Thermal effects refer to the absorption and scattering of the ultrasonic wave through the tissue, accompanied by energy attenuation. When sound energy is absorbed, it is converted to heat energy, the more energy is absorbed the more heat is generated. When the temperature rises above 43 °C, proteins and cells are destroyed, inducing apoptosis and necrosis [86], stimulating the body's immune response. The method of treating diseases by using the immune response generated by the thermal effect of ultrasound is called iSTT. On the other hand, mechanical effects include microstreaming, radiation forces, cavitation and sonoporation. Among them, the cavitation effect is divided into stable cavitation and inertial cavitation. Stable cavitation creates microstreaming, radiation forces and local thermal effects through a continuous cycle of expansion and contraction of the gas nucleus for therapeutic purpose [85,87]. Inertial cavitation means that the gas nucleus grows to the natural resonance size under large pressure, oscillates greatly, and collapses when it reaches the critical fluid point. The radiation forces and shock wave generated by the rupture of the gas nucleus will promote the release and penetration of drugs [12]. In addition, the cavitation effect can also lead to the sonoporations, which increases cell membrane porosity and permeability, thus increasing drug uptake, to achieve more efficient on-demand delivery of immune formulations [88]. The method of improving the efficiency of immune formulations delivery through the above mechanical effects of ultrasound to achieve tumor suppression effect is called iSMT. Extremely high temperatures and pressures are generated during inertial cavitation, resulting in chemical effects by causing sonoluminescence, tissue destruction, and pyrolysis of water molecules to form reactive oxygen species (ROS). At this point, if the sonosensitizer is added, it will absorb energy and undergoes electronic transition after ultrasonic irradiation, which is excited from the ground state to the excited state. Due to the instability of the excited state with high-energy, a large amount of energy will be released when it spontaneously returns to the ground state, and a series of reactions will occur with the surrounding substances such as O_2 to produce a large number of ROS [83]. The increased intracellular drug content and ROS produced by the energy transition can exert the killing effect to tumor cells, resulting in cell apoptosis or necrosis, and further inducing the generation of immune response, which is called iSDT.

In addition, there is a special mechanism for ROS generation. Under the action of ultrasonic mechanical stress, the deformation of the piezoelectric medium produces electron polarization, which catalyzes the redox reaction of surrounding H_2O, thereby producing ROS to exert a tumor-killing effect, which is called sonopiezoelectric therapy (SPT), and when combined with immunotherapy, it is named iSPT.

4. Nanomaterials combined with US in cancer immunotherapy

Due to the lack of targeting immune drugs, low bioavailability and delivery barriers such as dense tumor stroma, it is difficult for the simple combination of ultrasound and immune agents to completely improve the dilemma faced by tumor immunotherapy. In recent years, benefiting from the development of nanotechnology, the efficacy of ultrasound-mediated cancer immunotherapy has been further improved.

Nanomaterials can be used as carriers for drug delivery, and modified ligands or peptides on their surface can specifically target malignant tumors [89,90]. Some nanomaterials themselves have the properties of sonosensitizer, which can improve the efficacy of tumor treatment. Once administered, nanomaterials can specifically accumulate at the site of the lesion through enhanced penetration and retention effect or active targeting ability [1,91], and achieve controlled release of drugs and immune agents in target tumors through exogenous ultrasonic stimulation response, which can increase local drug concentration in tumors, reduce drug leakage, improve the response rate of immunotherapy such as ICB and CAR-T therapy in solid tumors and avoid systemic adverse reactions [92–94]. In addition, the immune system can be activated by the release of TAAs due to the destructive effects of ultrasound irradiation of microbubbles loaded with chemotherapy drugs and immune adjuvants, and ROS produced by ultrasound irradiation of nanomaterials such as liposomes and nanocomposites loaded with sonosensitizers or piezoelectric materials. Due to DAMPs release, calreticulin (CRT) accumulates in discrete regions of the plasma membrane, HMGB-1 is transported to the extracellular and nuclear space, and the expression level of HSP 70 is upregulated. By promoting DC maturation and T cell activation, proliferation and recruitment, the tumor microenvironment can be reshaped to effectively inhibit the growth of primary tumors, distant tumors and lung metastases.

Next, we will introduce the application of nanomaterials used with US to enhance biological effects in cancer immunotherapy, mainly including iSTT, iSMT, iSDT and iSPT.

5. iSTT for cancer

In recent years, photothermal therapy has attracted extensive attention due to its effect of inducing apoptosis and necrosis of cancer cells through thermal effects in response to near-infrared light (NIR light), releasing TAAs to activate the immune system, and playing the role of antitumor immunotherapy [95–101]. However, because of the shallow penetration of light (penetration depth of NIR-I light: $\leq$1 cm, penetration depth of NIR-II light: 3–5 cm) [101], it is not suitable for deep tumors. At this point, ultrasound has a greater clinical application prospect than NIR light because of its advantages of noninvasively, high tissue penetration and controllability. Moreover, ultrasound irradiation can be focused on the target lesion zone more precisely than NIR light irradiation, thus endowing iSTT with superior spatiotemporal selectivity and less normal tissue toxicity.

Among them, Focused ultrasound (FUS) is a treatment method that can ablate tumors by thermal and cavitation effects under a certain range of energy input. Low-energy FUS (LOFU) is able to generate heat energy in deep tissues, maintaining the temperature at 43 °C. It can increase capillary diameter, cell membrane permeability and tissue perfusion, thereby improving the efficiency of drug delivery. At the same time, it can also promote the infiltration of immune cells into tumor cells, enabling APCs to present antigens to DCs, activate CTLs and T cells, and exert antitumor effects [102].

Various mechanisms lead to insufficient activation of APCs, inhibition of DCs' presentation of antigens, and induction of reduced T cell reactivity to tumor antigens, which leads to inadequate immune response efficiency of the adaptive immune system. Bandyopadhyay et al. [102] used LOFU to generate mild non-lethal thermal and mechanical stresses in target tissues, thereby generating unique and more immunogenic tumor antigens, inducing the expression of stress proteins, improving the efficiency of tumor antigens in non-ablative treatment, and reversing immunosuppressive microenvironment induced T cell tolerance. *In vitro* and *in vivo* experiments showed that LOFU induced the redistribution of CRT in the cells and tumor tissues of melanoma, increased the expression levels of heat shock protein (HSP) 70, MCH-II

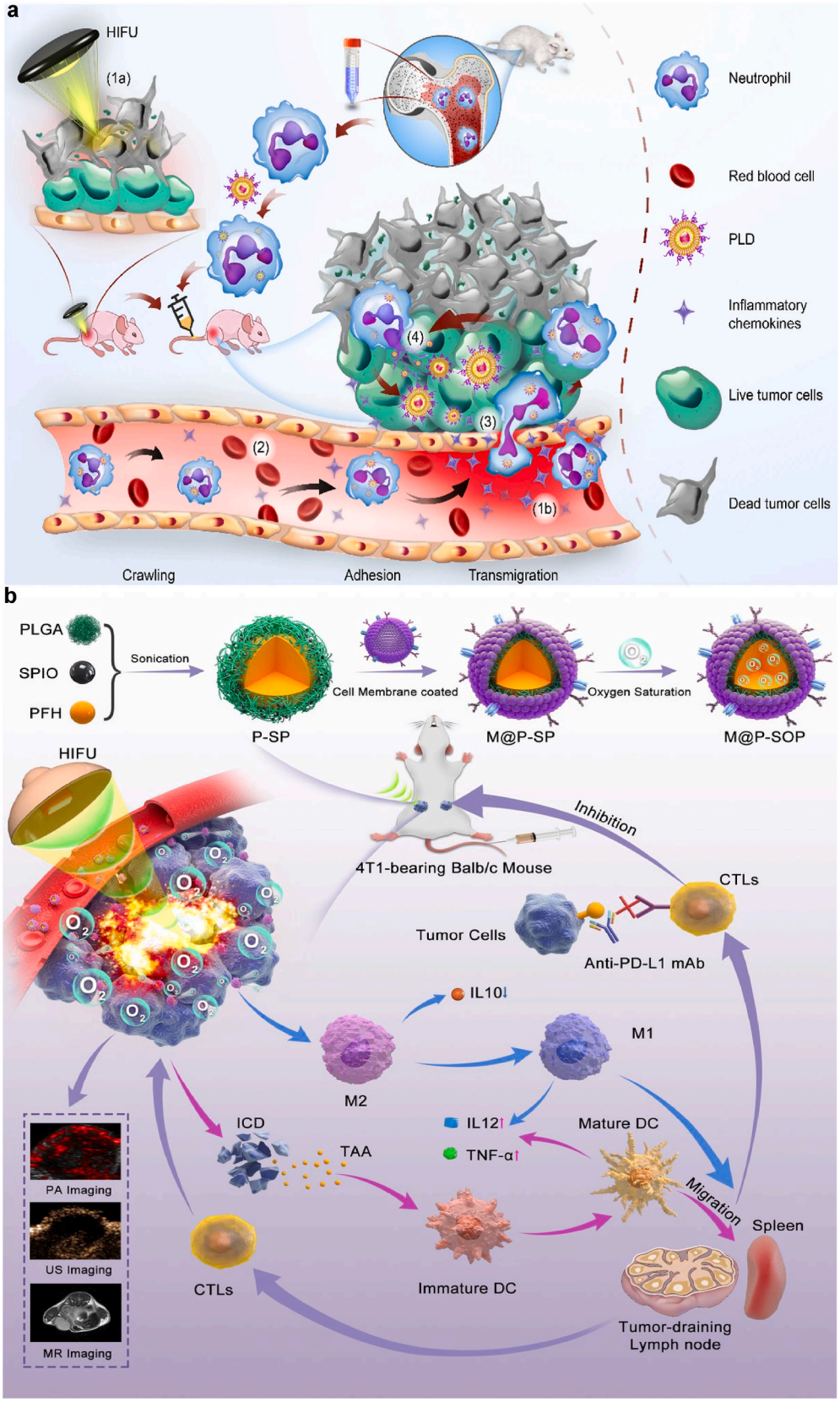

Fig. 3. The thermal effect of HIFU enhances immunotherapy. a) Schematic illustration for the construction of PLD@NEs and its mechanism to enhance immunotherapy. Reproduced with permission from Ref. [110]. Copyright 2022, Springer Nature. b) Schematic illustration for the construction of M@P–SOP and its mechanism to enhance immunotherapy. Reproduced with permission from Ref. [111]. Copyright 2023, BMJ Publishing Group Ltd.

and B7 proteins, promoted DCs maturation, and improved the effective presentation of tumor antigens. When LOFU was pretreated prior to ablative fractionated radiotherapy, it exerted a synergistic effect to control the growth of primary tumors, reduce the number of lung metastases, and extended relapse-free survival in mice.

As the sound pressure increases, the temperature rapidly rises above 60 °C, thermal ablation will occur, the tissue fragments produced by ablation activate the immune system through different immunogenic pathways. Tumor fragments and DAMPs after high intensity focused ultrasound (HIFU) thermal ablation can be used as in-situ vaccines to enhance antitumor immunity, can also activate DCs and CTLs by inducing Th1 immune response. In addition, HIFU plays an important role in balancing the tumor immunosuppressive microenvironment [103].

Although HIFU thermal ablation techniques have been approved for clinical treatment of prostate diseases and gynecological tumors [104–106], for malignant diseases, the risk of local recurrence after HIFU surgery remains high, which is related to the excessive thermal effect of HIFU resulting in partial inactivation of endogenous danger signals and limited ability to drive antitumor T cell responses.

In order to enhance the strong response of T cells to tumor cells by HIFU thermal ablation, the researchers used HIFU combined with chemotherapy to enhance the ablation effect and activate the systemic immune response. For example, Sheybani et al. [107] combined gemcitabine (GEM) and sparse-scanning thermal ablation FUS, which attenuates myeloid suppressor cells, significantly inhibited the growth of primary triple-negative breast cancer (TNBC) and prolonged overall survival in mice with lung metastasis. In addition, the adaptive immune system also significantly increased the levels of $CD4^+$ and $CD8^+$ T lymphocytes compared with the sham operation group and GEM group alone, accompanied by a moderate increase in the percentage of $Foxp3^+$ Treg cells, in addition to a 2–5 folds increase in the percentage of NK and B cells, which may be the reason for the decreased mortality associated with TNBC lung metastasis.

Another study [108] showed that when in situ thermal ablation combined with nano-adjuvant R837 and αCTLA-4 monoclonal antibody, the ratio of $CD8^+$ T cells to Tregs in distant tumors of CT26 tumor-bearing mice increased by 5 times, triggering a strong antitumor response, the number of effector T memory cells in the spleen of mice increased significantly, the serum level of IFN-γ increased significantly, and the TNF-α increased slightly. Within 40 days after the combination treatment, the distant tumor disappeared completely, effectively inhibiting the metastasis. 40 days after HIFU ablation of the primary tumor, CT26 cells were re-inoculated, exhibiting a strong immune response. Observation at 80 days after tumor rechallenge showed that this combined treatment strategy effectively inhibited tumor recurrence, and the survival rate of mice reached 80 %.

Aside from that, studies have shown that the inflammatory response induced by HIFU plays an important role in antitumor immunity. The release of intracellular proteins after HIFU ablation in advanced pancreatic cancer leads to an increase in serum LDH levels, which activates the subsequent inflammatory cascade, resulting in increased levels of leukocytes and C-reactive proteins, and corresponding increased levels of IL-6, which is associated with enhanced activity of macrophages and T-lymphocytes in the acute phase [109]. Shen et al. [110] exploited this HIFU thermal ablation-related inflammatory response to develop an inflammation-prone neutrophil-mediated nanodrug PLD@NEs. Experiments with Hepa1-6 cells and corresponding tumor-bearing mice showed that the surface-specific modified nanocarriers targeted the inflammatory environment caused by HIFU thermal ablation after intravenous injection. PEGylated liposome doxorubicin (PLD), a chemotherapeutic drug carried by neutrophils, infiltrated the tumor through the concentration gradient of chemokines, overcoming the biological barrier encountered by the traditional drug delivery route. When PLD@NEs reached the tumor, PLD was released, followed by internalization by tumor cells, and the drug concentration in the residual tumor after HIFU thermal ablation was increased, thereby effectively inhibiting the recurrence of the tumor (Fig. 3).

Researchers [111] have also carefully designed a new type of oxygen-carrying biomimetic perfluorocarbon nanocapsules (M@P–SOP) to realize the efficient synergistic effect of HIFU and immunotherapy. Under the homing effect of tumor cell membrane, M@P–SOP targeted the tumor and utilized the high temperature generated by HIFU treatment to stimulate M@P–SOP to release oxygen to alleviate the anoxic microenvironment of the tumor, repolarizing M2 macrophages into antitumor M1 macrophages. At the same time, the cavitation effect produced by oxygen further enhanced the ICD induced by HIFU, stimulated the maturation of DCs, and activated $CD8^+$ T cells. In conjunction with αPD-L1, it improved the reactivity of T cells, activated systemic immune response, and inhibited the growth of tumors in primary and distal in 4T1 tumor models (Fig. 3). Similarly, Kuai et al. [112] developed a PFOB nanoemulsion loaded with manganese dioxide nanoparticles, which utilized the high temperature generated by HIFU to release oxygen from perfluorooctyl bromide (PFOB) and enhance the effect of HIFU thermal ablation during the blasting process. At the same time, MnO_2 consumes GSH, further enhanced HIFU-induced ICD, and reversed the tumor immunosuppressive microenvironment by inducing DCs maturation and promoting the activation of $CD4^+$ and $CD8^+$ T cells. The synergistic effect of GSH depletion and HIFU inhibited the growth of 4T1 tumors and lung metastases.

All in all, the above strategies open a new chapter in iSTT of tumors, which will provide a new paradigm of clinical significance for tumor immunotherapy due to the clinical applicability of HIFU therapy.

6. iSMT for cancer

In addition to the thermal effects of ultrasound used in immunotherapy, the mechanical effects of ultrasound also play an important role in antitumor immunotherapy, known as iSMT. Under the powerful mechanical effect induced by ultrasound, biomolecules and cells undergo drastic changes, which are used to enhance the efficacy of antitumor immunotherapy and inhibit tumor growth. Among them, the most widely studied mechanical effects are the cavitation effects of mechanical HIFU (M-HIFU), and ultrasound combined with microbubbles. In addition, studies also have shown that genetically encoded gas vesicles and minimally invasive ultrasound needles can trigger sonomechanical effect to improve the effectiveness of cancer immunotherapy.

6.1. M-HIFU

Mechanical HIFU (M-HIFU), unlike thermal HIFU (T-HIFU), which causes protein denaturation and coagulation necrosis by raising the temperature of the lesions to 60–85 °C, it is through high-intensity ultrasound with low duty cycles to oscillate and rupture the gaseous components in the tissue, producing cavitation, resulting in mechanical damage at the subcellular level.

M-HIFU generates immunotherapeutic effects through two mechanisms. One is to generate steam bubbles within a few milliseconds, which oscillates after bursting, damaging tissues by mechanical fractionation, initiating adaptive immunity and TNF-induced necrosis signaling pathways, and promoting the release of DAMPs and HMGB-1. Eventually, immunogenic death occurs [113,114]. The other is that the bubbles interact with US, creating shockwaves that destroy cells and lead to the production of cellular debris, thereby initiating an immune response. Renske et al. observed the immunomodulatory effects of M-HIFU and T-HIFU in the EG7 lymphoma model. By characterizing the RNA, DNA, and proteins of HIFU-generated cell fragments, they found that M-HIFU treatment produced unique tumor fragments with obvious signs of fragmentation, significantly down-regulated expression levels of the immunosuppressive factors TGF-β and IL-10, and enhanced DC-induced T cell activation when combined with CpG (TLR9 agonist)

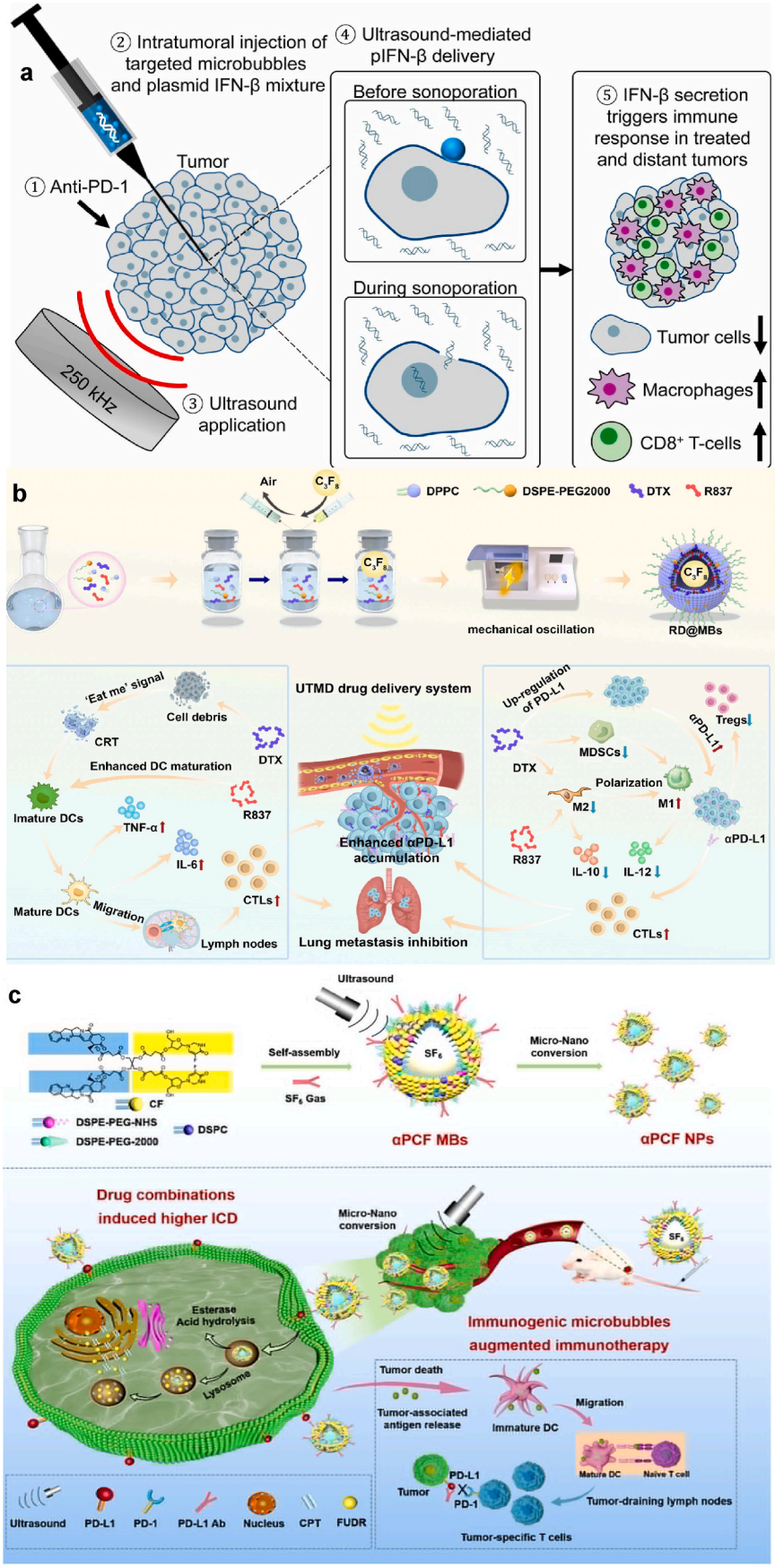

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Fig. 4. Illustration of UTMD-mediated gene transfection and drug delivery to enhance immunotherapy. a) Schematic illustration of mechanism of UTMD-mediated gene transfection. Reprinted with permission from Ref. [130]. Copyright 2020, PNAS. b) Schematic illustration of UTMD-mediated drug delivery to enhance immunotherapy. Exhibited the preparation process of RD@MBs and mechanism of *in vivo* antitumor immune response induced by RD@MB combined with αPD-L1. Reprinted with permission from Ref. [132]. Copyright 2023, Springer Nature. c) Schematic illustration of UTMD-mediated drug delivery to enhance immunotherapy and the fabrication of immunogenic αPCF MBs and US mediated micro−nano conversion. Reprinted with permission from Ref. [133]. Copyright 2022, American Chemical Society.

[115]. During the same period, Shinya et al. from Duke University used a bilateral tumor model to observe the effects of systemic antitumor immunotherapy induced by T-HIFU and M-HIFU. The results showed that M-HIFU was more effective than T-HIFU against treated tumors and untreated distal tumors, and were further validated in two other mouse models. In addition, they observed long-term immune memory effects in the M-HIFU treated mice. Using flow cytometry, immunohistochemistry, and single-cell RNA sequencing, they further demonstrated that the physical destruction of M-HIFU reshaped macrophages in the tumor, promoting their development to the immune stimulating M1 subtype [116]. The combination of αPD-L1 antibodies or consumption of $CD4^+$ T cells containing regulatory T cells significantly enhanced cell-mediated antitumor immunity and tumor growth inhibition, in which $CD8^+$ T cells and NK cells played an important role as effector cells [116].

According to the different duration of the pulses and the size of the bubbles, M-HIFU is divided into histotripsy and boiling histotripsy [117,118]. Regardless of the mode of action, M-HIFU can release DAMPs that mediate intratumoral $CD8^+$ T cell infiltration and secretion of pro-inflammatory cytokines and chemokines stimulate local intratumoral innate and adaptive immune responses, combined with ICIs, can enhance the effect of cancer immunotherapy, and inhibit distant metastasis [114,119,120].

6.2. Ultrasound-targeted microbubble destruction

The amount of steam bubbles generated by M-HIFU monotherapy within a few milliseconds is limited. If the cavitation effect is increased by increasing sound pressure blindly, it will pose a safety hazard to the normal tissues around the target. At this point, ultrasound-targeted microbubble destruction (UTMD) shows unique advantage in terms of safety by inducing cavitation through gas nuclei provided by microbubbles. It utilizes microjets, shock waves and free radicals generated by ultrasonic cavitation to cause a series of changes in vascular endothelial cells, such as enhancing the permeability of endothelial cells, dilatating blood vessels and enhancing blood supply, *etc.*, which will promote drug penetration, improve the efficiency of gene transfection, regulate the expression of cytokines, reshape the immunosuppressive microenvironment, and further improving the effect of antitumor immunotherapy [121]. Meanwhile, microbubbles also act as contrast agents to display the drug delivery process in real time.

Studies have shown that malignant solid tumors promote the formation of tumor neovascularization by inducing the release of various pro-angiogenic and anti-angiogenic factors, thus ensuring the nutrient supply of the tumor and promoting the rapid growth of the tumor. Vascular endothelial growth factor (VEGF) can promote endothelial cell division and support endothelial cell migration, induce the expression of endothelial cell adhesion molecules, mobilize bone marrow-derived cells, and promote the formation of tumor blood vessels [122]. These abnormal neoplastic blood vessels play a key role in promoting tumor growth and metastasis. Therefore, it is very important to destroy tumor neovascularization and reduce tumor perfusion to improve the therapeutic effect.

Wu et al. [123] developed a novel therapeutic strategy combing UTMD and αPD-L1, which destroyed abnormal tumor neovascularization through cavitation effect, thus depleting tumor blood supply, and promoted DCs' maturation through up-regulating of pro-inflammatory factors such as IL-12 and TNF-α and down-regulation of VEGF expression. The levels of DCs and $CD8^+$ T cells in the DLNs and tumor tissues were significantly increased, and the T lymphocyte mediated immune response was further induced, while the TME was remodeled to make it sensitive to αPD-L1, and the growth of subcutaneous 4T1 breast cancer and MC38 colorectal cancer in mice was significantly inhibited [123,124].

However, rather than destroying tumor blood vessels, Lin et al. [125] suggested that UTMD played an antitumor role by promoting tumor blood vessels normalization. UTMD activated vascular endothelial cells and promoted vascular normalization by increasing pericyte coverage and stimulating tumor associated macrophage repolarization. In this way, the blood perfusion of the pancreatic cancer can be increased, and the growth and metastasis of the tumor can be inhibited.

In addition, mechanical stress of UTMD can also promote the overexpression of HSP60 by dilating blood vessels, induce DCs maturation by binding to scavenger receptor or HSP receptor LOX-1 expressed on DCs, and mediate tumor antigen exposure and promote cytokine secretion, which can trigger adaptive immune responses mediated by T cells [126–128].

Recent studies have shown that UTMD mediated gene transfection technology can effectively transfect genes into tumor and stromal cells, generate immune activating cytokines, and enhance T cell infiltration. Compare with small microbubbles (1.27 ± 0.89 μm), large microbubbles (4.23 ± 2.27 μm) have higher gene transfection efficiency after low frequency ultrasound (250 kHz) irradiation [129,130]. When combined with immune ICIs, this technology can further enhance the effect of immunotherapy through various mechanisms. For example, Professor Ferrara's team from Stanford university transfected plasmid DNA encoding IFN-β into solid tumors, with UTMD *in vitro*, IFN-β secretion was as high as 153 pg/10^6 cells, which was significantly higher than that of untreated, ultrasound free and microbubbles free groups (<1pg/10^6 cells). The frequency of macrophages and $CD8^+$ T cells was increased by IFN-β, triggering systemic immune response of tumors in primary and distant [130] (Fig. 4). Encouraged by the efficiency of microbubble-mediated DNA delivery, Qin et al. [131] used cationic lipid microbubbles loaded with soluble PD-1 (sPD-1) and miR-34a to achieve gene transfection by UTMD. Under the action of UTMD, miR-34a down regulated the apoptosis suppressor gene Bcl-2, promoted cell apoptosis, cooperated with sPD-1 to induce NK cells, and reestablished antitumor activity. Excellent antitumor immunotherapy effect was obtained in U14 cervical cancer subcutaneous xenograft mice.

Although various immunotherapy strategies have been clinically used to modulate the tumor immunosuppressive microenvironment and successfully suppress many cancers, such as non-small cell lung cancer and melanoma, *etc.*, the current immunotherapy still has a limited response rate. An adequate response occurs only when the tumor expresses enough neoantigens and is pre-infiltrated by enough effector T cells. Our study showed that camptothecin (CPT) and floxuridine (FUDR), when released in 1:1 M ratio in the TME, can synergistically trigger an immunogenic tumor phenotype, sensitizing αPD-L1 and further reshaping the immunosuppressive microenvironment. Microbubbles self-assembly by camptothecin-floxuridine conjugate and αPD-L1 can further improve the accumulation of drugs in tumor tissues and effectively reduce off-target side effects under the action of sonoporation and micro-nano conversion caused by UTMD, thus providing a safe and universal treatment strategy for tumor immunotherapy [134,133] (Fig. 4).

Similarly, Zheng et al. designed microbubbles loaded with chemotherapy drug docetaxel (DTX) and immune adjuvant R837, under

noninvasive irradiation by US, DTX was released to induce tumor cell death, and dying tumor cells release TAAs and T cell stimulators, such as CRT, CD80 and CD86, activating antitumor immune responses. At the same time, DTX also had the function of immune regulation, up-regulating the expression of PD-L1 on tumor cells, promoting the uptake of αPD-L1, inducing the repolarization of M2 phenotype to M1 in macrophages, and reducing the proportion of MDSCs, thereby realizing efficient tumor chemoimmunotherapy [132] (Fig. 4).

6.3. Genetical encoded gas vesicles (GVs)

In addition to using microbubbles to achieve the mechanical effects of ultrasound, Professor Mikhail Shapiro's team reported that they used genetically encoded GVs, gas-filled protein nanostructures, to combine with tumor homing bacteria to produce effective mechanical therapy in the tumor core under the inertial cavitation generated by low-frequency ultrasound. When combined with αCTLA-4 and αPD-L1, it can produce better antitumor efficacy [135].

Low-frequency ultrasonic pulse was used to break and open the GVs, releasing the gas they contain in the form of nanobubbles, and drive cavitation. At sufficiently high amplitudes, these bubbles undergo rapid growth and violent collapse during inertial cavitation, releasing strong local mechanical effects. Here, engineered GVs acted as remotely driven cell-killing and tissue-destroying agents, cracking engineered genetic cells and releasing molecular payloads to produce local mechanical damage on command. They injected A20 lymphocytes under the skin of immunocompetent mice to create subcutaneous solid tumors. To improve tumor homing ability, they expressed GVs in *Escherichia coli* Nissle *1917* (EcN) and injected these engineered EcN intravenously into mice, which were able to target and penetrate into the solid tumor core from the systemic circulation. 3 days later, L-arabinose was administered systematically to induce GVs expression. 2 days after inducing tumor homing cells to express GVs in situ, the tumors were exposed to FUS under ultrasound guidance, while the ICIs such as αCTLA-4 and αPD-L1 were injected. The results showed that insonated tumors colonized by GVs-expressing bacteria slowed tumor growth by about 3 times compared to the control group, and the median survival was also extended from 16 days to 37 days. These results indicate that the combination of genetically encoded GVs with targeted bacteria can provide an effective iSMT effect on the tumor core, and the combination with ICIs can produce better antitumor effects.

6.4. Ultrasound needles

It is well known that one of the key factors for the poor therapeutic effect of ICIs is insufficient tumor lymphocyte infiltration, and therapies that can destroy tumors, expose tumor antigens, and promote tumor lymphocyte infiltration may have synergistic effects with ICIs [37,136].

In addition to the mechanical effects generated by the gas nucleus, the ultrasonic horn, an acoustic device with an operating frequency of 20–40 kHz and a pressure amplitude of more than several hundred kilopascals at the horn tip, also produce direct mechanical destruction and strong cavitation, which provides the possibility of destroying tumors by increasing tumor antigen exposure to improve the efficiency of the immune response [137]. Tang et al. [138] modified the ultrasonic horn to prepare a new type of device, which is called the ultrasonic needle (UN). By inducing antitumor immunity through mechanical destruction of UN, and combining with αPD-L1, it provides a new idea for ultrasound-assisted immunotherapy.

The vibration of the needle mechanically destroys the local tumor, and the vibration process is accompanied by the formation of bubble clouds, which provide the cavitation nucleus for the violent cavitation. At the same time, in the process of UN treatment, radiation force, shock wave and microjet will also be generated, causing secondary damage to the tumor. This mechanical disruption induces immunogenic death, exposing tumor antigens and releasing DAMPs, where CRT accumulates in discrete regions of the plasma membrane, HMGB-1 is transported to the extranuclear and extracellular space, and the expression level of HSP70 is upregulated. All of these can promot DCs migration and maturation, activate T cells, and increase $CD8^+$ T cells infiltration.

Through a series of experiments, Tang et al. further demonstrated that DCs dependent antigen presentation played an important role in the induction of $CD8^+$ T cell dependent antitumor immunity by UN treatment. But the antitumor effect of UN was not limited to the immune effect, but also be related to the direct mechanical destruction of tumor tissues. UN combined with αPD-L1 significantly inhibited the growth of primary and distal tumors, and significantly increased the median survival time of tumor-bearing mice.

7. iSDT for cancer

Ultrasound produces sonoluminescence, pyrolysis and cavitation bubble rupture under inertial cavitation effect, activates the sonosensitizers to produce electrons, and catalyzes redox reactions of surrounding substrates (H_2O and O_2) to generating various ROS ($^1O_2$, $\bullet O_2^-$, and $\bullet OH$), induces cancer cell death and releases DAMPs, further activates the immune response [139,140]. Significantly different from thermal and other mechanical effects, iSDT requires the use of sonosensitizers, usually some inorganic or organic small molecule compounds, which can penetrate deep into the lesion and trigger the production of ROS under the action of ultrasound, making the treatment more precise.

Its mechanism is similar to that of photodynamic therapy, but it is superior in the treatment of deep tumors due to its higher tissue penetration. It is worth noting that inflammation and activation of the immune system occur in the lesions after SDT, because high levels of ROS oxidize the cell's lipid bilayer membrane, DNA and protein structures, causing cellular oxidative stress, which can induce ICD while eliminate the primary tumor, release TAAs, and promote the maturation of DCs [141]. However, compared to direct damage from mechanical and thermal effects, the immune response induced by SDT is limited by a relatively slow and mild oxidative death process, and various immunosuppressive pathways can also lead to immune escape. For example, tumor cells highly express immune checkpoint ligands, bind to immune checkpoint proteins on the surface of T cells, turn off activated T cells, and evade immune surveillance. The tumor immunosuppressive microenvironment can protect tumor cells from being destroyed by immune cells and promote tumor growth. Based on these mechanisms, researchers developed strategies that combine SDT with multiple immunotherapies to further improve the efficiency of SDT-induced ICD and activate effective antitumor immune responses by regulating the tumor immunosuppressive microenvironment.

7.1. iSDT synergistically enhances the efficacy of ICB therapy

Due to greater tumor heterogeneity, tumors with less surface expression of PD-L1 had a lower response rate to ICB. SDT can not only cause immune response and activate the body to produce more immune cell, but also stimulate tumor cells to express more PD-L1, thereby improving the delivery efficiency of αPD-L1 and the response rate of ICB, synergistically improving the effect of immunotherapy [142].

Currently, ICIs based on the PD-1/PD-L1 pathway are also widely used to modulate antitumor immune responses. Normally, PD-1 is expressed on the surface of T cells, and its ligand PD-L1 is expressed on the surface of APCs. The combination of PD-1 and PD-L1 plays a crucial part in maintaining immune homeostasis by inhibiting the production of immune cytokines and the proliferation of T cells. However, many tumor cells overexpress PD-L1, depleting CTLs and thus evading immune surveillance. At this time, αPD-1/PD-L1 can restore the immune surveillance function of CTLs, and when combined with SDT-induced ICD and CTLs infiltration, systemic antitumor immune response can be successfully induced. Chen et al. [143] demonstrated that the combination of $TiSe_2$ nanosheet-mediated SDT and αPD-L1 effectively

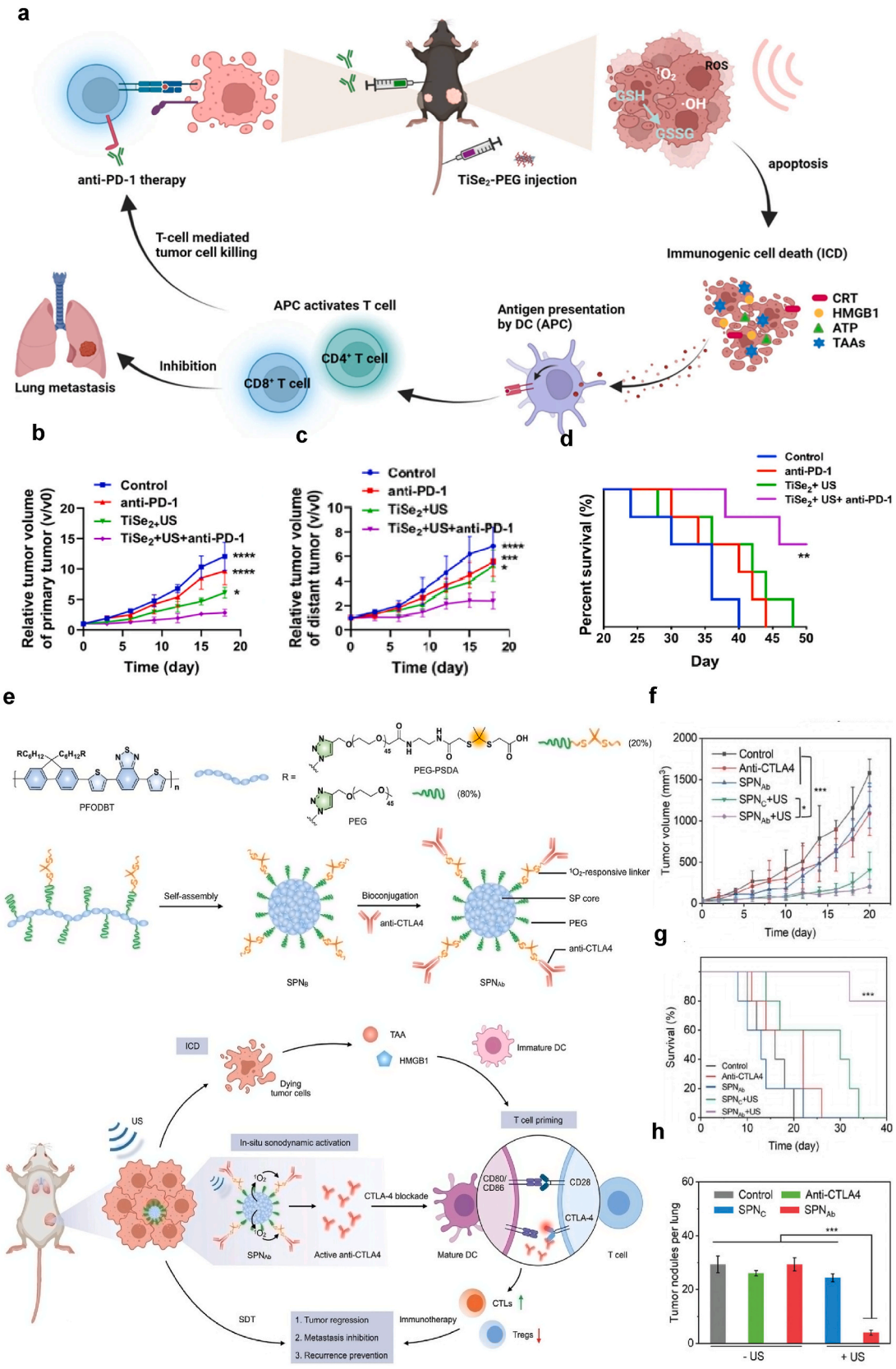

Fig. 5. Illustration of SDT synergistically enhances the efficacy of ICB therapy. a) Schematic illustration of TiSe2 nanosheets-mediated SDT binded with αPD-L1 to enhance immunotherapy, b) primary tumor growth, (c) distant tumor growth and survival rates for mice bearing metastatic Pan02-luci tumors after different treatments. Reprinted with permission from Ref. [143]. Copyright 2022, Springer Nature. e) Schematic of the synthesis of the SPNAb and its mechanism for synergistic enhancement of αCTLA-4. f) tumor growth, g) survival rates and h) numbers of metastatic nodules per lung for mice bearing 4T1 tumors after different treatments. Reprinted with permission from Ref. [146]. Copyright 2022, Wiley-VCH.

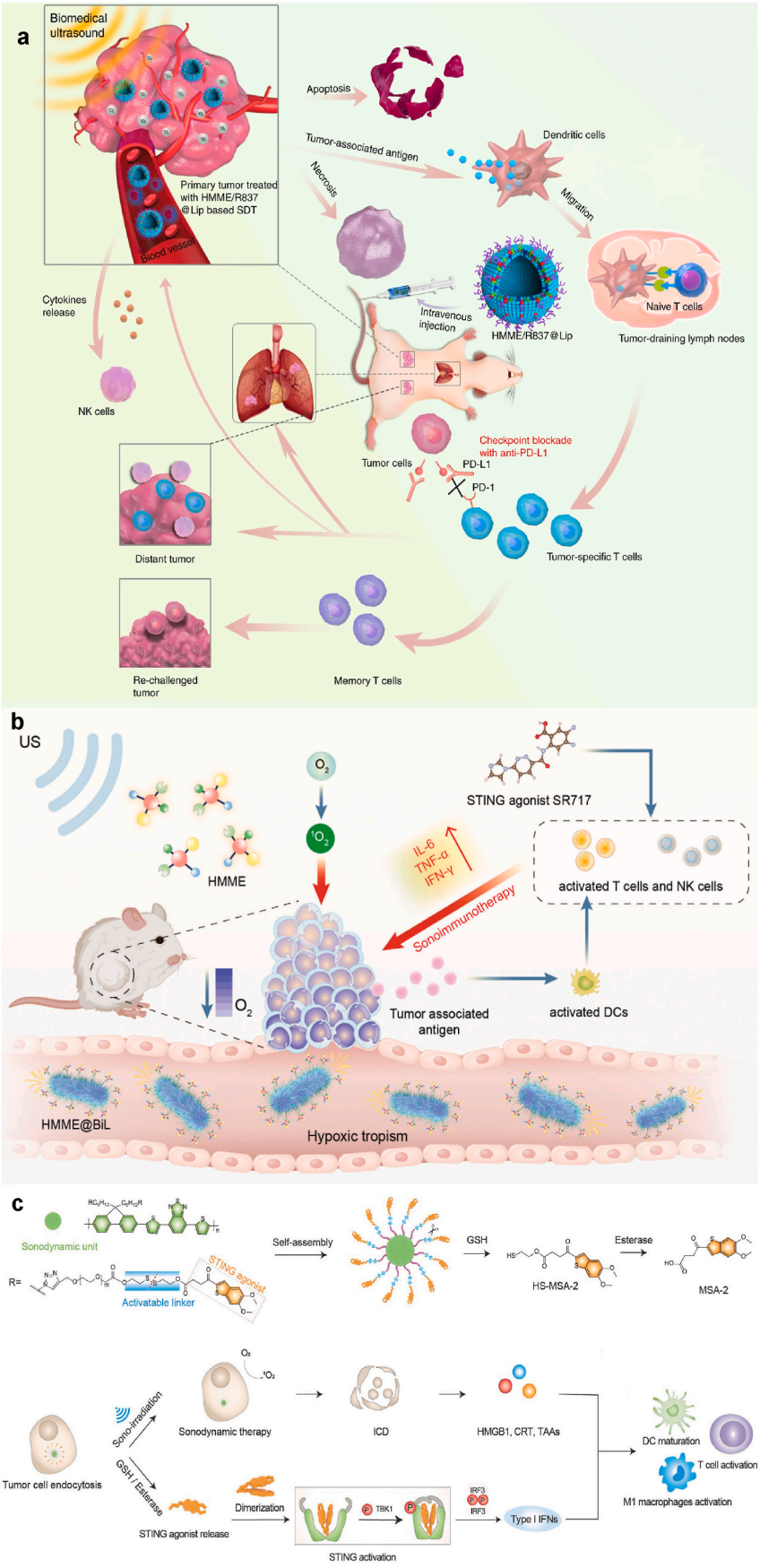

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Fig. 6. Illustration of SDT synergistically enhances the efficacy of immune system modulators by TLRs and STING-agonists. a) Scheme of antitumor immune responses induced by combined SDT with TLRs R837 and αPD-L1. Reprinted with permission from Ref. [13]. Copyright 2022, Springer Nature. b) Scheme of mechanism for iSDT enhanced by HMME@BiL with STING-agonists. Reprinted with permission from Ref. [148]. Copyright 2022, Wiley-VCH. c) Synthesis of PSPA and its mechanisms to synergistically enhance immunotherapy. Reprinted with permission from Ref. [149]. Copyright 2023, Wiley-VCH.

activated an antitumor immune response by inducing ICD through a series of experiments. $TiSe_2$ nanosheets can generate a large amount of ROS under ultrasound irradiation regardless of normoxic or hypoxic conditions, drived the maturation of DCs by inducing the ICD of tumor cells, promoted the secretion of cytokines such as TNF-α, IL-12P40 and IL-6, activated the infiltration of $CD8^+$ T cells in distant tumors. It also reduced the number of Tregs in distant tumors. Through the enhancement of cell mediated systemic immune response, the growth of distant tumors and lung metastasis were also inhibited while the growth of primary pancreatic cancer was inhibited (Fig. 5). However, since PD-L1 is also widely present in normal organs in the body, in order to avoid immune related side effects caused by off-target toxicity of αPD-L1, scholars have proposed various ideas, such as αPD-L1 is conjugated by MMP2-cleavable peptide linker and self-assembly into nanomaterials [144], and the use of PD-L1 peptide antagonist ^{D}PPA [145], which is more stable and less costly, effectively inhibits immune escape through these safer ways.

In addition to αPD-1 and αPD-L1, αCTLA-4 is also a classic ICB, which can also combine with SDT to enhance the antitumor effect. In 2011, the αCTLA-4 antibody, ipilimumab, was approved by the FDA as the first ICI for the treatment of melanoma, ushering in the era of cancer immunotherapy [147]. Currently, ICIs are one of the most promising immunotherapy methods for solid tumor treatment, which can restore the cytotoxic effect of T cells on tumor cells by blocking the interaction between tumor cells and T cells. SDT combined with ICIs can further induce immunogenic death, promote DCs maturation and CTLs infiltration, and play a powerful role in antitumor immunotherapy.

Pu and his team [146] prepared the sono-immunotherapeutic nanobodies (SPN_{Ab}) by coupling the αCTLA-4 antibodies to the semiconducting polymers through $^1O_2$-cleavable linker using semiconductor polymer as sonosensitizer. Under ultrasound irradiation, SPN_{Ab} produced $^1O_2$, exerted sonodynamic therapy effect and induced ICD while releasing αCTLA-4, triggering in situ immune checkpoint blockade. With the synergistic effect of promoting the proliferation of CTLs and the depletion of Tregs, the tumor inhibition rate of SPN_{Ab}-mediated iSDT was 86.7 %, which was 3.5 times higher than that of SPN_{Ab} group without ultrasound irradiation and 2.8 times higher than that of free αCTLA-4 group, and inhibited the occurrence of lung metastasis. At 30 days after the first tumor inoculation, 4T1 cells were inoculated subcutaneously again with SPN_{Ab} + US treated and untreated Naïve mice, respectively. The tumor growth was significantly inhibited, and survival was significantly prolonged compared with the untreated group. Overall, SPN_{Ab}-mediated iSDT achieved regression of primary tumor, effectively inhibited metastasis, and produced lasting immune memory effect to prevent recurrence (Fig. 5).

Collectively, the combination of SDT and ICIs can enhance the antitumor iSDT effect, and has great clinical application potential.

7.2. iSDT synergistically enhances the efficacy of immune system modulators

Immune system modulators, also known as immune adjuvants, show great potential in tumor immunotherapy and have a wider applicability by activating innate immune responses, cytokines and chemokines compared to the lower response rate of ICBs. The immune adjuvants that have been developed so far are toll-like receptor agonists (TLRs) and STING agonists. However, these agonists have limited water solubility and poor pharmacokinetics. Systemic administration of TLRs and STING agonists will cause serious side effects in non-target sites, and its ability to effectively activate DCs *in vivo* is limited, which impede its application. Therefore, the combination of agonists and sonosensitizers to prepare nanoparticles can not only improve the biological distribution, but also collaboratively improve the therapeutic effect.

7.2.1. Toll-like receptor agonists

Members of the Toll-like receptors (TLRs) family contain intracellular Toll/IL-1 receptor (TIR) domains that dimerized when foreign substances enter, activating TIR, which in turn binds to the MyD88 gene or aptamer protein to activate the innate immune cascade. Imiquimod (R837), as a TLR-7 agonist, can be taken up by DCs and produce inflammatory cytokines such as IFN-α and IFN-γ, which promote the maturation of DCs through the MyD88 pathway. However, R837 has limited water solubility and poor pharmacokinetic properties. Systemic administration of R837 will cause serious side reactions in non-target sites, and its ability to effectively activate DCs *in vivo* is limited, which impede its application. To this end, Yue et al. [13] used liposomes as carriers to encapsulate the sonosensitizer HMME and R837 to construct the nanoplatform HMME/R837@Lip. After systemic administration, HMME/R837@Lip had a higher accumulation and a longer retention time in tumors. Under ultrasound irradiation, the in-situ tumor antigen produced by HMME together with R837 exerted a tumor vaccine-like effect, activated the adaptive immune response, and killed tumor cells through the secretion of IL-6, TNF-α and mature DCs. After combined with αPD-L1, the level of infiltrating $CD8^+$ T cells in tumor was significantly increased. Verified by 4T1 breast cancer and CT26 colorectal cancer mouse models, the above strategies not only inhibited the growth of primary tumors, distal tumors, and metastases, but also had long-term immune memory effects. In CT26 mouse model, 75 % (6/8) of the mice were resistant to rechallenge after the combination treatment, while all of the control groups died within 26 days of vaccination (Fig. 6).

In addition to traditional drug delivery strategies, sonosensitizers can also be linked to TLRs for tumor iSDT via GSH-responsive chemical bonding. Lei et al. [150] linked reduced methylene blue to R837 through disulfide bonds, and autonomously assembled MB-R837-PEG (MRP) nanoparticles by amphiphilic polymer C18PMH-PEG. When MRP reached the tumor tissue, MB and R837 were released under the action of TME, which improved the treatment efficiency and effectively reduced the occurrence of side effects. In order to verify the efficacy of MRP in stimulating the maturation of DCs, after co-incubating with CT26 cells for 12 h, the supernatant was incubated with mouse BMDCs for 16 h, and the proportion of $CD80^+CD86^+$ in $CD11C^+$ DCs in MRP group was increased significantly. After MRP injection and ultrasound irradiation in tumor-bearing mice, T cells, M1 macrophages and DCs were infiltrated into the tumor, and mature DCs in inguinal lymph nodes were significantly upregulated. Unfortunately, PD-L1 expression levels within tumors were also upregulated, limiting the effectiveness of immunotherapy. At this time, combined αPD-L1 further promoted the maturation of DCs in tumors and lymph nodes, the infiltration of T lymphocytes and the polarization of M1 macrophages, and upregulated the levels of IL-12p70, IL-6 and TNF-α in tumors and lymph nodes. Finally, the complete elimination of tumors in mice was achieved, the survival time of mice was extended, and no tumor regeneration was achieved during the re-challenge, and the systemic immune effect after local treatment was realized.

7.2.2. STING agonists

The cell signaling pathway stimulating factor (STING) of interferon gene plays a crucial part in the activation of innate immune response, which promotes the maturation of DCs and drives the activation of T cells and NK cells through the production of cytokines and chemokines.

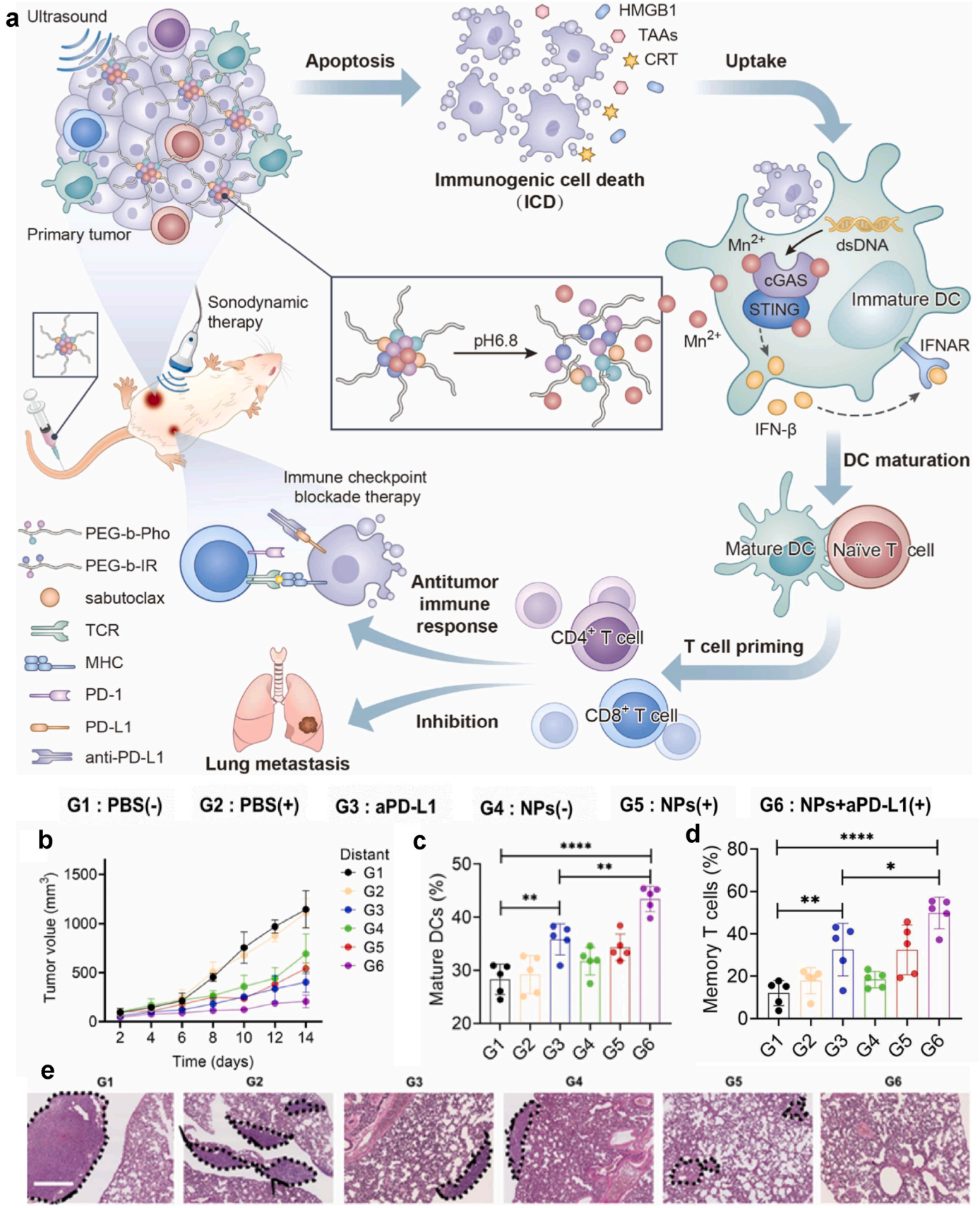


Fig. 7. Illustration of SDT synergistically enhances immunotherapy by activating STING pathway through Mn^{2+}. a) The mechanism diagram of PIMS NPs promoted DCs maturation and sensitized ICB therapy. b) Tumor volume growth curves for distant tumors, c) mature DCs in DLNs, d) memory T cells in spleen and e) H&E staining images of lung metastasis in 4T1 bearing mice after different treatments. Reprinted with permission from Ref. [151]. Copyright 2022, Elsevier.

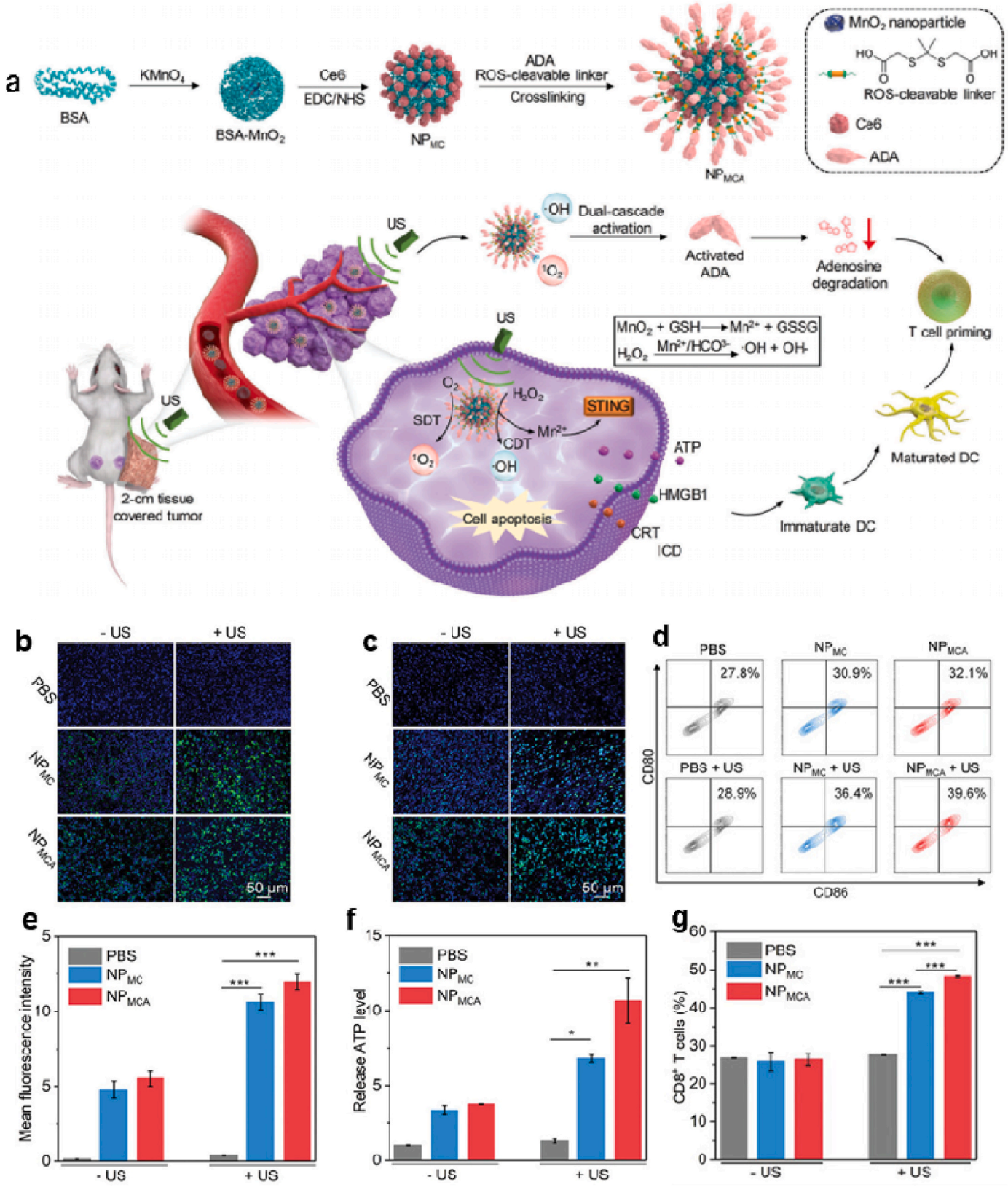


Fig. 8. Illustration of dual-cascade activatable nanopotentiator (NPMCA) for enhancing immunotherapy. a) Scheme of NPMCA Synthesis and its antitumor immune mechanism. Immunofluorescence staining of b) CRT and c) HMGB1 in primary tumors covered by chicken breast tissue. d) Flow cytometry analysis of DCs in LNs of mice after different treatments. e) Relative fluorescence intensity of HMGB1 and f) relative ATP levels in primary tumors covered by chicken breast tissue after different treatments. g) Number of $CD8^+$ T cells in distant tumors after different treatments. Reprinted with permission from Ref. [152]. Copyright 2023, Wiley-VCH.

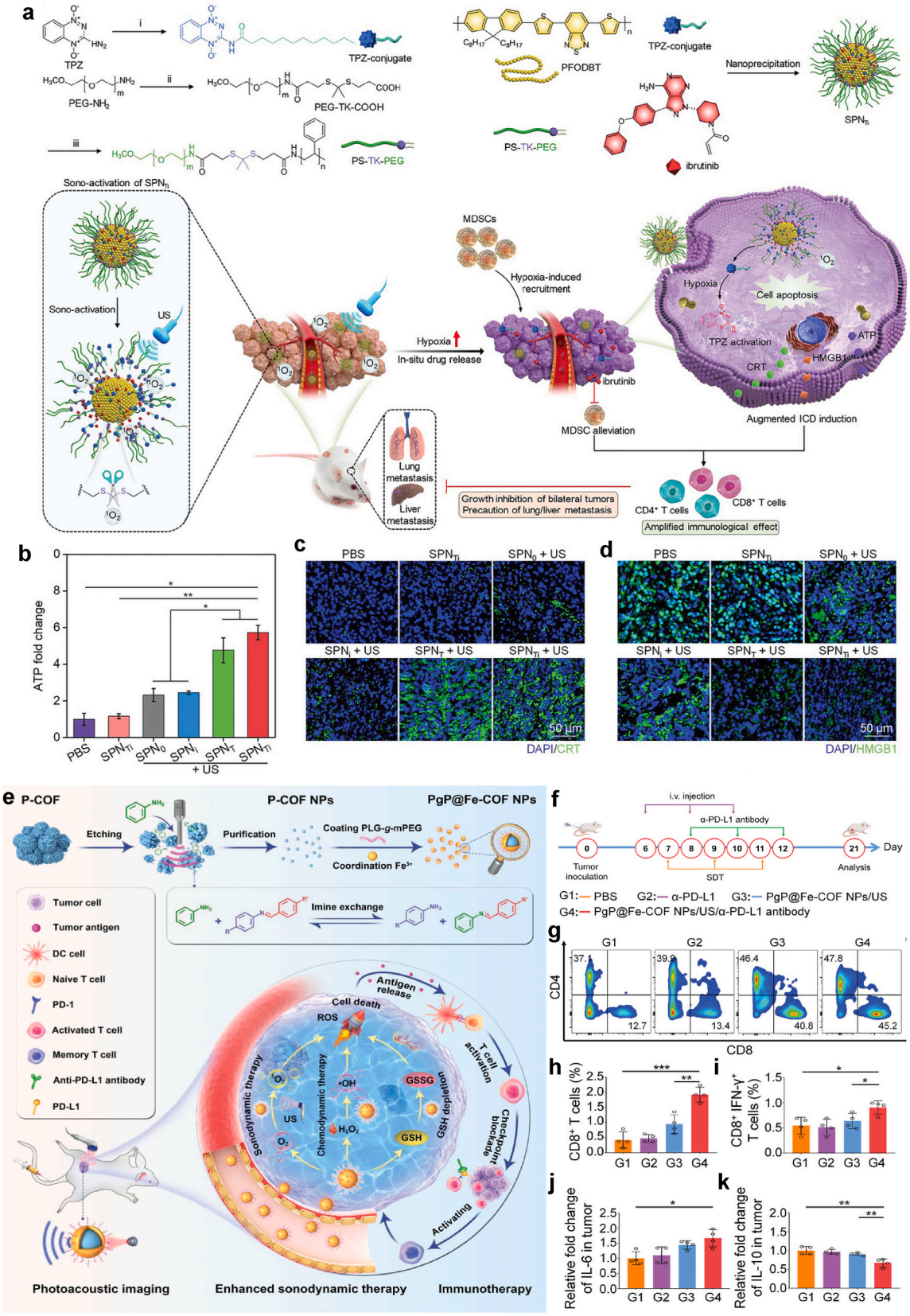


Fig. 9. Illustration of enhancing immunotherapy by utilizing tumor physiological environment in coordination with SDT. a) Scheme of the formation of SPNTi and its antitumor immunotherapy mechanism. b) Intratumoral ATP levels, Tumor c) CRT and d) HMGB1 immunofluorescence staining images in mice under different treatments. Reprinted with permission from Ref. [154]. Copyright 2023, Wiley-VCH. e) Scheme of the formation of PgP@Fe–COF NPs and its antitumor immunotherapy mechanism. f) Treatment regimen of the combination therapy. g) The flow cytometry results of $CD4^+$ and $CD8^+$ T cells in the tumors. The quantitative analysis of h) $CD8^+$ T cells and i) $CD8^+$ IFN-γ^+ T cells in the tumors. The relative change of j) IL-6 and k) IL-10 in tumors. Reprinted with permission from Ref. [155]. Copyright 2022, Wiley-VCH.

Based on this theory, the researchers have developed several strategies to enhance iSDT by activating the STING pathway. Lu et al. [148] enhanced the iSDT effect of *bifidobacterium* encapsulated HMME by intraperitoneal injection of STING agonist SR717, effectively eliminating primary tumors and metastases (Fig. 6). However, after intraperitoneal injection, STING agonists activated the STING pathway in normal tissue, leading to immune-related adverse events (irAEs). In order to effectively reduce the occurrence of irAEs, Pu et al. [149] attached STING agonist MSA-2 to semiconductor polymer sonosensitizer PFODBT through GSH-responsive chemical bonding to obtain PSPA. PSPA accumulated into the tumor through EPR effect. Under the action of high GSH level in the tumor, MSA-2 was released to activate the STING pathway, significantly increased the secretion of IFN-β and IL-6, promoted the maturation of DCs, and activation of T cells, NK cells and M1 macrophages together with SDT-induced ICD. In the mouse model of bilateral tumors, the primary tumor and distal tumor in the PSPA + US group were effectively inhibited, and the immunofluorescence staining of tumor sections showed that caspase-3 was significantly upregulated, karyopyknosis and nuclear fragmentation appeared obvious in HE stains. Rechallenged tumor model showed that the growth of tumors in the PSPA + US group was significantly inhibited, and the number of lung metastases was significantly reduced compared with the saline group (Fig. 6).

In addition, Mn^{2+} can also independently activate the STING pathway, secrete IFN-β, promote the maturation of DCs, and synergize with IR-780-mediated SDT, showing obvious antitumor effects. When further combined with αPD-L1, the growth of distant tumors and lung metastasis were significantly inhibited, and the number of memory T cells in the spleen was 1.6 times higher than that in the free PD-L1 group, showing a better immune memory effect [151] (Fig. 7). As a paradigm, Han et al. [152] developed a dual-cascade activatable nano-enhancer NP_{MCA}. This nano-enhancer was formed by the adenosine deaminase ADA coupled to Ce6-conjugated MnO_2 by ROS cleavable linker. Under ultrasound irradiation, Ce6 and Mn^{2+}-mediated SDT and CDT produced ROS, resulting in double cascade cleavage of NP_{MCA}, release ADA, reshaped adenosine metabolism, and improved the efficiency of ROS-induced ICD. At the same time, Mn^{2+} upregulated the STING pathway to further guide the development of the immunosuppressive microenvironment in the direction of "immune hot". In the bilateral tumor bearing mouse model of 4T1, the inhibition rate of primary tumor and distal tumor were 95.8 % and 62.8 % respectively in the NP_{MCA} + US group. The number of DCs, $CD4^+$ T cells, $CD8^+$ T cells and $CD8^+$ T cells in the DLNs in the group treated with NP_{MCA} + US was significantly higher than that in the group treated without US, and the levels of cytokines IFN-γ and TNF-α were significantly increased, which further verified the improvement of the efficiency of antitumor immunotherapy. The number of DCs, $CD4^+$ T cells, $CD8^+$ T cells in the DLNs and the $CD8^+$ T cells in the distal tumor in NP_{MCA} + US group was significantly higher than that in the group without US treatment. The significant increase in cytokine IFN-γ and TNF-α levels also further verified the improvement of the efficiency of iSDT (Fig. 8).

Overall, the delivery of sonosensitizers and immune adjuvants through appropriate strategies to achieve reasonable integration while enhancing the effect and avoiding immune-related adverse events is a promising cancer treatment strategy.

7.3. iSDT synergies with TME remodeling to enhance immunotherapy

Immunosuppressive TME (acidity, hypoxia, high GSH content and vascular disorder) and immunosuppressive cells (M2 macrophages, Tregs and MDSCs) will significantly affect the efficacy of immunotherapy. Utilizing and remodeling immunosuppressive TME, combined with the therapeutic and immune effect of iSDT, will help to synergically improve the therapeutic effects of tumors, inhibit tumor recurrence and metastasis.

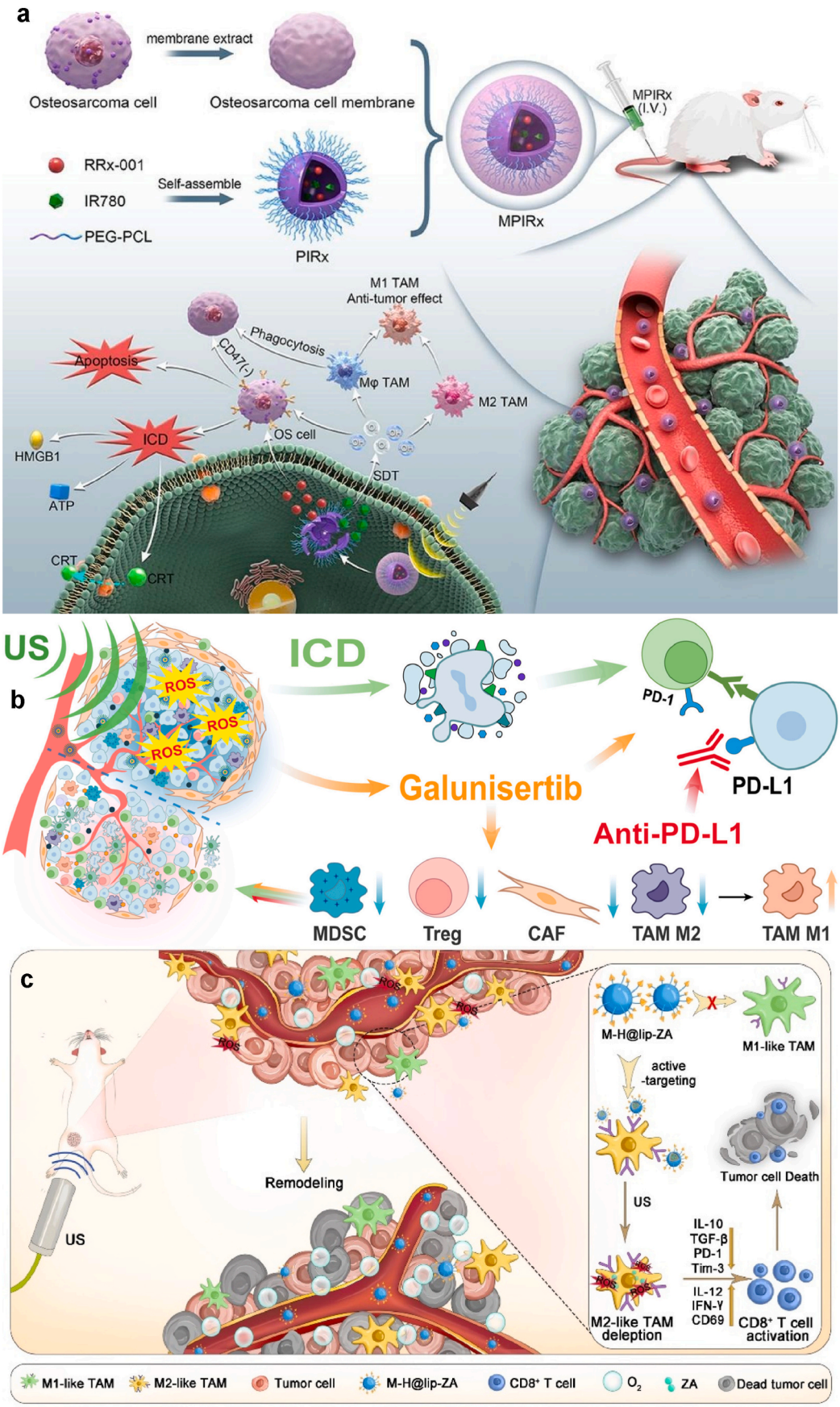
7.3.1. Physiological factors

SDT plays a certain role in inducing ICD and activating immune system activity. However, due to its mechanism characteristic of consuming O_2 to produce ROS, it will further aggravate tumor hypoxia and cause SDT resistance. Tirapazamine (TPZ) is a hypoxia-activated cytotoxic drug, and its ability to induce DNA double strand breaks under hypoxia is about 300 times stronger than that under normal oxygen conditions, which provides a theoretical basis for the combined use of SDT and TPZ. Zhao et al. [153] proposed to introduce sonosensitizer Ce6 and TPZ into pH-sensitive liposomes. Meanwhile, in order to target hypoxia induced platelet associated DAMPs, improve the therapeutic effect and reduce lung metastasis, they used red erythrocyte-platelet hybrid membranes to camouflage the liposomes. After systemic administration, the acidic microenvironment destroyed the structure of liposomes and released Ce6 and TPZ. After local ultrasound irradiation, Ce6-mediated SDT produced ROS, and the aggravated hypoxic microenvironment of tumors activated TPZ and induced DNA breakage. This synergistic effect enhanced the occurrence of ICD. Since biomimetic bait only retained the function of PLT, but it could not carry out PLT-mediated metastasis, and the high level of HMGB1 induced by SDT and chemotherapy further interfered with platelet activation, effectively inhibiting lung metastasis of melanoma.

Coincidentally, another team [154] adopted a similar strategy, they encapsulated the semiconductor sonosensitizers PFODBT, the anti-cancer drug TPZ and the MDSCs targeting drug ibrutinib in SPNTi, in which the carrier was a $^1O_2$-cleavable amphiphilic polymer. After SPNTi administration, O_2 was consumed by ultrasound irradiation to produce ROS, and the lysis of nano-polymers released TPZ and ibrutinib in tumors, then the severely hypoxic microenvironment activated TPZ and enhanced the generation of ICD, while ibrutinib alleviated the recruitment of MDSCs induced by hypoxia. Thus, the efficacy of antitumor immunotherapy can be improved by targeting the immune escape of MDSCs. The 4T1 bilateral tumor model *in vivo* showed that this strategy effectively inhibited the growth of orthotopic tumor, distal tumor, liver metastasis, and lung metastasis, and achieved the effect of enhanced iSDT (Fig. 9).

The antioxidant GSH, which is rich in tumor cells, can also lead to SDT resistance, so the strategy of consuming GSH will improve the efficiency of SDT-induced ICD. As a paradigm, Wang et al. [155] prepared P–COF NPs containing the sonosensitizer porphyrin by imine-based molecular exchange etching method, and coordinated Fe^{3+} to the porphyrin unit to obtain PgP@Fe–COF NPs, which achieved GSH consumption capacity, and enhanced SDT-induced ICD in coordination with chemo-dynamic therapy. In order to verify the GSH consumption capability of PgP@Fe–COF NPs, they used 1,10-phenanthroline (Phe) probe to observe. When PgP@Fe–COF NPs were co-incubated with GSH and Phe, the absorption of UV–vis uptake at 512 nm increased significantly, indicating that Fe^{3+} consumed GSH and reduced to Fe^{2+}, weakening the reducing TME. However, enhanced SDT increased the expression of PD-L1 on the tumor surface, and they further combined with αPD-L1 to effectively inhibit tumor growth, metastasis and recurrence in 4T1 mouse models (Fig. 9).

In addition, due to the large amount of ROS produced by SDT, the deoxygenation signaling pathway based on nuclear factor erythroid 2-related factor 2 (Nrf2) rapidly responds to ROS, limiting the function of SDT. At this time, Wan et al. [145] envisioned to down regulate the expression of this protein through Nrf2-siRNA transfection to improve the anti-tumor effect of SDT, so they developed a nanoparticle that co-delivered Nrf2-siRNA and IR-780, and used TAT peptide to further improve the transfection and SDT capabilities. TIR@siRNA with TAT peptide can perform nuclear targeting SDT and had a higher tumor-killing effect on CT26 cells. Gene silence of Nrf2-siRNA inhibited Nrf2 up-regulation after SDT, blocked redox balance regulation, activated mitochondrial apoptosis pathway, improved immunosuppressive TME by inducing ICD. This system further combined with the αPD-L1 peptide ^{D}PPA-1 to activate the immune system, effectively wiping out



(caption on next page)

Fig. 10. Illustration of enhancing immunotherapy by altering tumor immunosuppressive cells. a) Scheme of reshaping macrophages in coordination with SDT through MPIRx to enhance immunotherapy. Reprinted with permission from Ref. [156]. Copyright 2023, Wiley-VCH. b) Scheme of inhibiting TGF-β by NCG cooperated with SDT to enhance immunotherapy. Reprinted with permission from Ref. [157]. Copyright 2023, Elsevier. c) Scheme of depleting M2 macrophages targeted by M-H@lip-ZA along with SDT to enhance immunotherapy. d) M2-like TAMs and e) PD-L1 expression on M2-Like TAMs after different treatments. The level of f) IL-10, g) TGF-β, h) IL-12 and i) IFN-γ in serum from mice receive treatments. Reprinted with permission from Ref. [158]. Copyright 2023, Elsevier.

the primary tumor and inhibiting the metastasis of colorectal cancer.

Taken together, these strategies based on redox balance regulation provide a new way to improve the efficiency of iSDT.

7.3.2. *Immunosuppressive cells*

There are plenty of Tumor associated macrophages (TAMs) in the TME, which are important cells to promote tumor growth and metastasis while have become important targets for antitumor therapy. In fact, TAMs, as duplicitous in the immune environment, play bidirectional roles, which is determined by their different polarization types. Typically, TAMs are polarized into M1 pro-inflammatory macrophages and M2 anti-inflammatory macrophages, with M1 exerting antitumor effects and M2 exerting opposite effect. In the TME, TAMs tend to polarize towards M2, which inhibits the proliferation and activation of CTLs and promotes the growth of tumor cells. Therefore, strategies to increase the content of M1 or deplete M2 targeted are expected to improve the therapeutic outcomes. As one of the paradigms, Gong et al. [156] developed MPIRx, a nanodrug that effectively controlled macrophage migration for Osteosarcoma (OS) lung metastasis. They encapsulated the sonosensitizer IR780 and CD47 inhibitor RRx-001 into PEG-PCL micelles and coated OS cell membrane to increase the targeting ability. MPIRx was irradiated with ultrasound to cause more migration of monocytes to OS cells and polarized to M1 macrophages under the promotion of SDT. Transwell, qPCR, and immunofluorescence of tumor sections showed that MPIRx plus ultrasound irradiation increased the polarization of M1 macrophages. Although the mechanism of this effect was not fully understood at present, MPIRx nanomaterials provided a strategy for macrophage-related immunotherapy through oxidative stress generated by SDT and the regulation of TAMs and CD47 in tumor tissue, which can successfully eliminate OS and inhibit refractory lung metastasis (Fig. 10).

The other team [158] reprogrammed TAMs by constructing strategies that targeted and deplete M2 macrophages. They constructed nanoparticles with Zoledronic acid (ZA), a drug that promoted apoptosis of macrophages, and used the peptide M2pep (sequence: yeqdpwgvkwwy-) as a targeted group to deliver drugs to M2 macrophages, inducing apoptosis of M2. M-H@lip-ZA exerted a synergistic effect on the SDT induced by sonosensitizer HMME and M2 depletion, it downregulated the immunosuppressive factors IL-10 and TGF-β, upregulated the immunostimulatory factors IL-12 and IFN-γ, and promoted the normalization of tumor blood vessels, increased hemoperfusion of tumor tissue. $CD8^+$ T cells in tumor tissues were increased (7.4 times higher than those in PBS group), so as to better exert the role of antitumor immune response. After intravenous administration and ultrasound irradiation, the tumor growth of 4T1 tumor bearing mice was significantly inhibited (90 ± 3 %), and the survival rate of mice was significantly improved (80 %) on the 45th day, which further demonstrated that ZA and SDT synergically accelerate the consumption of M2 macrophages and achieve effective antitumor immunotherapy (Fig. 10).

7.3.3. *"Immune cold" to "immune hot"*

As early as 2009, experts raised the issue of "immune hot" and "immune cold" of tumors, where "immune hot" are tumors infiltrated by T lymphocytes, while "immune cold" are tumors that are difficult to penetrate by immune cells, mostly because of the presence of immunosuppressive cells and immunosuppressive factors such as MDSCs, Tregs and TGF-β. Among them, TGF-β not only stimulates cancer-associated fibroblasts (CAFs) to produce collagen, forming a natural barrier for CTLs infiltration, but also inhibits the differentiation of CTLs and the maturation of DCs, resulting in poor immunotherapy effect. In order to transform "immune cold" tumor into "immune hot" tumor, Huang et al. [157] prepared a nanodrug NCG that encapsulated TGF-β inhibitor galunisertib (Gal) and Ce6. On the one hand, NCG-mediated SDT produced ROS, which caused ICD, and activated the innate T lymphocyte immune response through immune stimulation signals such as CRT and HMGB1. On the other hand, NCG released TGF-β inhibitors in the acidic TME, inhibited the differentiation of MDSCs by inducing Smad2/3 signaling pathway, induced M1 polarization, destroyed the immune barrier established by CAFs, and increased the infiltration of effector T cells, thus successfully transforming "immune cold" tumors into "immune hot" tumors to improve the therapeutic effect of αPD-L1. Transwell experiments *in vitro* showed that own to the effect of Gal, tumor cell fragments in the NCG + US group further promoted the maturation of $CD80^+CD86^+$ cells (40.50 % *vs* 29.07 %), released more IL-12p70 and TNF-α, enhancing the antitumor immune response. CT26 tumor bearing mice further verified the iSDT effect of NCG + US, and the results showed that the tumor growth inhibition rate was the highest in the treatment group, and the number of liver metastases was the lowest, indicating that NCG-mediated SDT and inhibition of TGF-β had potential application value in the treatment of "immune cold" tumors (Fig. 10). Another team constructed PFH liposomal nanodroplets containing IR-780 and STING agonist DMXAAs, after oxygen saturation, IDP@O_2 were obtained. The O_2 provided by PFH alleviated tumor hypoxia and improved SDT effect. TAAs generated by SDT synergistically played the role of orthotopic vaccines with DMXAAs, transforming "immune cold" TNBCs into "immune hot" tumors by promoting the maturation of DCs, the secretion of cytokines, and the infiltration of CTLs. When IDP@O_2 was combined with US, it improved the tumor killing efficiency of αPD-L1. Experiments of bilateral subcutaneous 4T1 tumor-bearing have shown that IDP@O_2 accumulated at the tumor site, effectively inhibited the growth of tumors in situ and unirradiated distal tumors, produced long-term immune memory effects [159].

7.4. *iSDT synergies with other methods to enhance immunotherapy*

Although various studies have reported that SDT can cause ICD, a specific variant of regulatory cell death, it is still difficult to achieve the intensity of effective elimination of tumors. Therefore, various strategies to promote SDT-mediated ICD have received extensive attentions.

7.4.1. *Enhanced cell apoptosis*

Apoptosis is a highly regulated form of cell death that typically occurs via exogenous pathways, mitochondrial pathways, and endoplasmic reticulum stress pathways. Among them, mitochondria are the site of ATP production, which plays a central role in the regulation of ROS production and apoptotic cell death. By targeting mitochondria, it is possible to enhance the efficacy of SDT. Accordingly, Luo et al. [160] selected triphenylphosphonium (TPP) to modify nMOFs to achieve the purpose of targeting mitochondria. Meanwhile, in order to avoid monocyte-mediated drug clearance and improve drug accumulation in tumors, tumor cell membranes were used to wrap nanomaterials. Zr-TCPP (TPP)/R837@M based on TPP-coupled porphyrins and simultaneous delivery of TLR7 agonists were prepared. This cascade bioreactor achieved reliable tumor targeting and antitumor activity while retained the efficient drug delivery properties of nMOF. SDT induced TAAs release in situ, initiated vaccine-like activity, especially after combination with R837, triggering a robust immune response by inducing the maturation of DCs, and the secretion of IL-6, IL-12p40 and

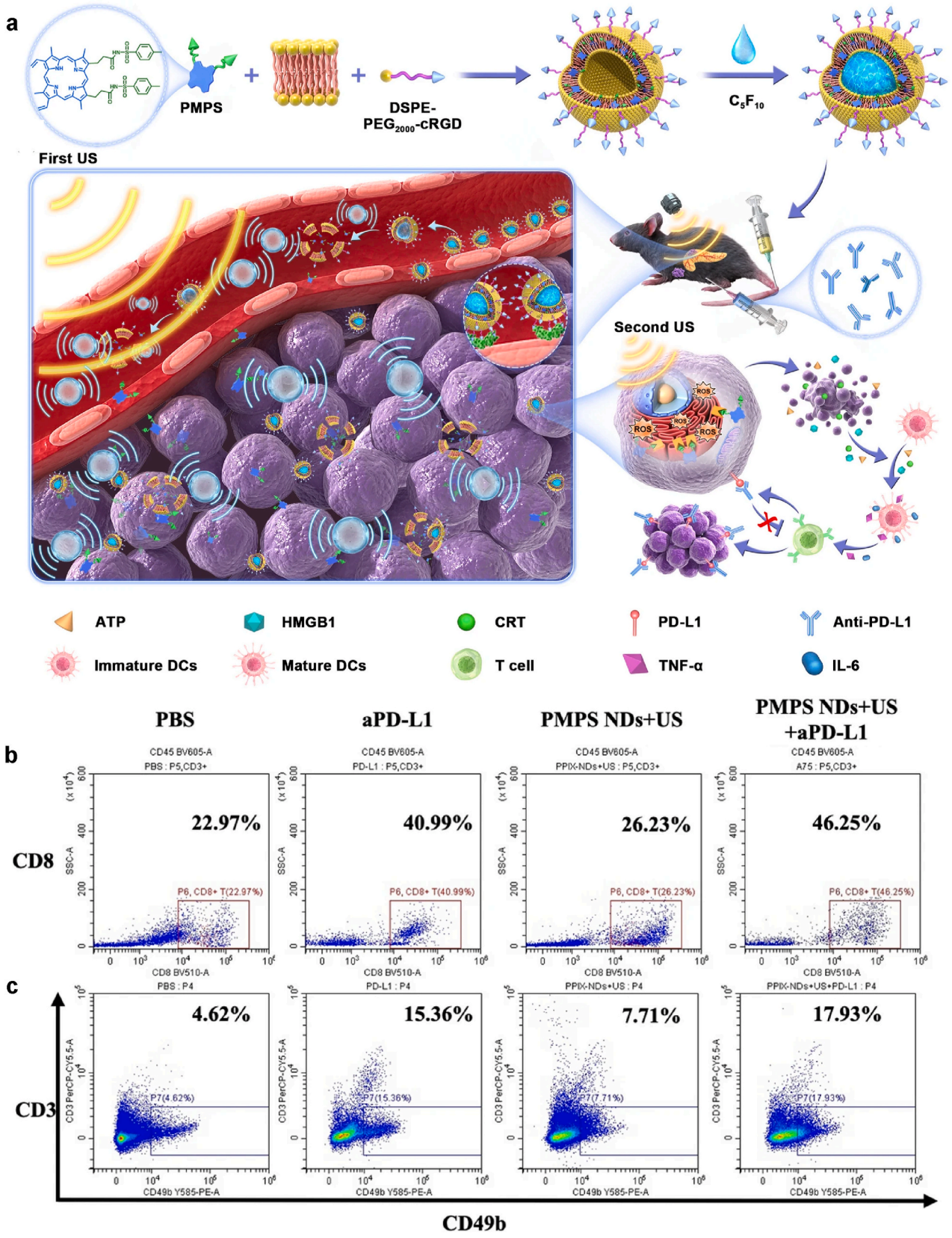


Fig. 11. Illustration of enhancing immunotherapy by enhanced apoptosis in coordination with SDT. a) Scheme of PMPS synthesis route and its antitumor immune mechanism *in vivo*. The flow-cytometry results of b) $CD8^+$ T cell and c) NK cells in tumors. Reprinted with permission from Ref. [161]. Copyright 2022, Springer Nature.

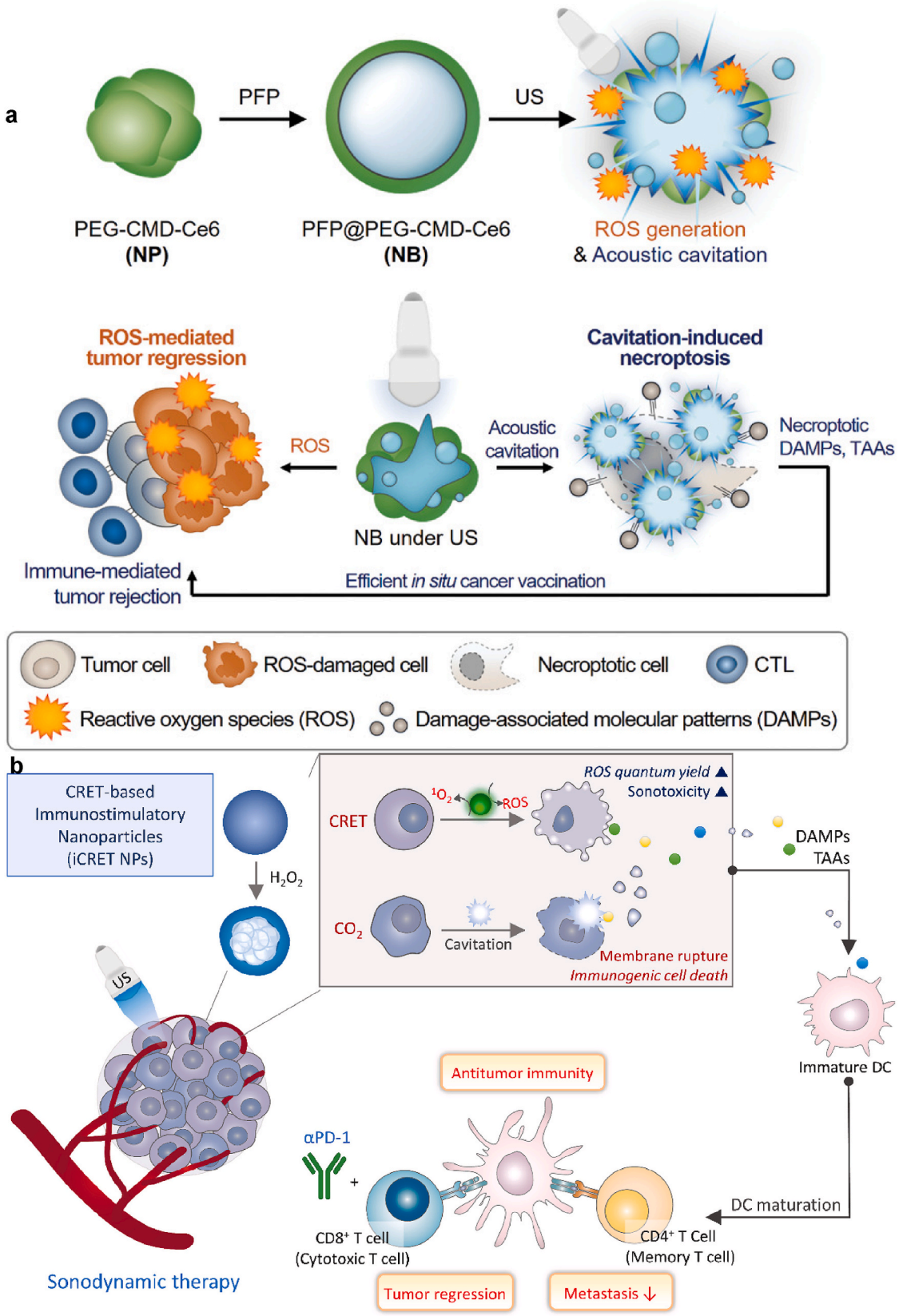


Fig. 12. Illustration of enhancing immunotherapy by necroptosis in coordination with SDT. a) Scheme of necroptosis-inducible NBs for antitumor immune response. Reprinted with permission from Ref. [162]. Copyright 2020, Wiley-VCH. b) Scheme of iCRET NPs led to enhanced immune responses by CRET. Reprinted with permission from Ref. [163]. Copyright 2022, Elsevier.

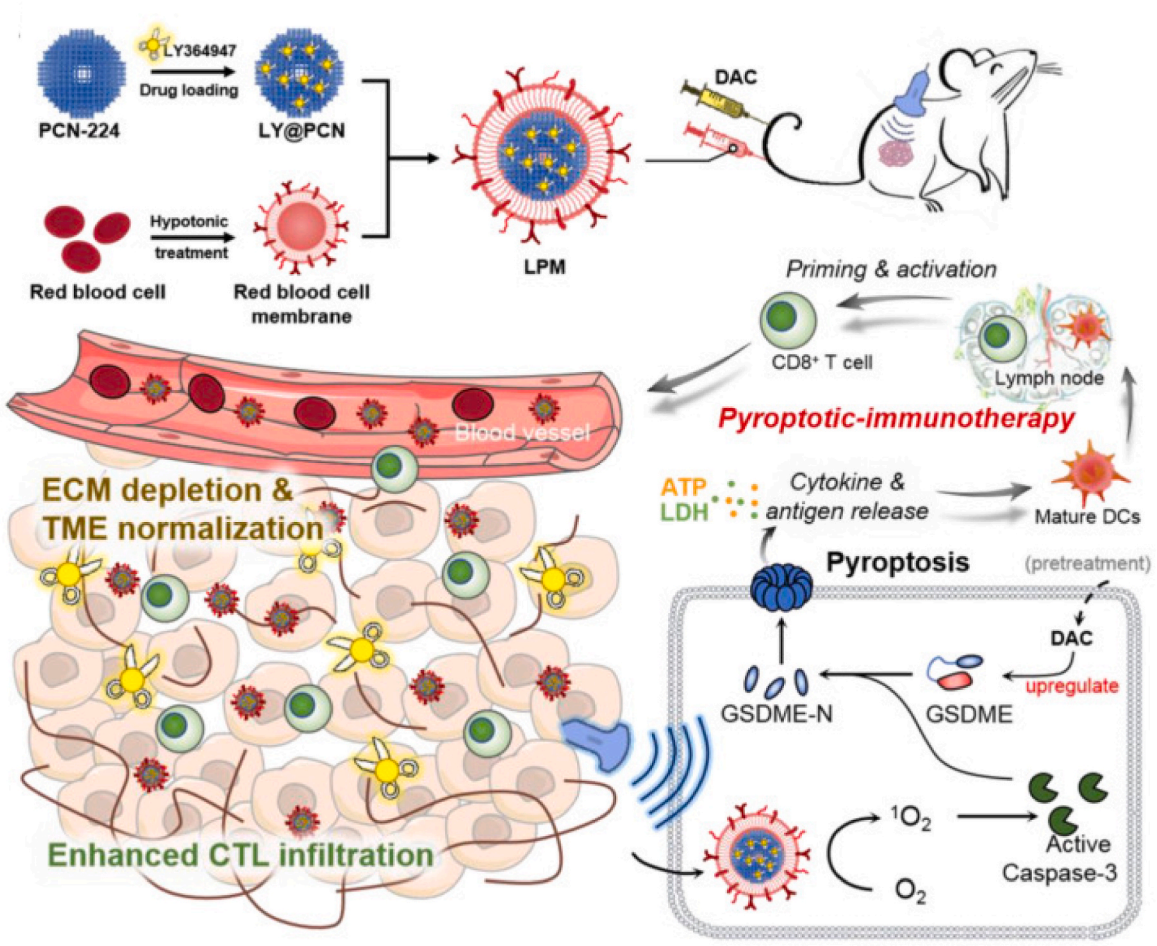


Fig. 13. Illustration of enhancing immunotherapy by pyroptosis in coordination with SDT. Scheme of iSDT induced by the nanostimulator LPM. Reprinted with permission from Ref. [164]. Copyright 2023, Ivyspring.

TNF-α. The experimental results showed that Zr-TCPP (TPP)/R837@M + US had a stronger ability to induce DCs maturation (9.36 ± 0.82 %) than non-mitochondrial targeted Zr-TCPP/R837@M + US (6.15 ± 1.49 %). When combined with αCTLA-4, the infiltration of $CD8^+$ T cells within the tumor was further increased. This strategy effectively inhibited the growth of orthotopic tumors, distal tumors and lung metastases in 4T1 tumor models, and established a durable immune memory effect, effectively preventing tumor reattack after the elimination of the primary tumor.

Due to the relatively short effective distance and duration of ROS, and the presence of antioxidant enzymes in the body that counteract the ROS produced by SDT, Chen et al. [161] prepared a cavitation assisted endoplasmic reticulum targeted sonodynamic nanodroplet PMPS NDs by rotary evaporation using PPIX and MPSU as raw materials, in which MPSU can bind to sulfonylurea receptors in the endoplasmic reticulum. After intravenous administration, the nanodroplets gathered in the tumor. Under US irradiation, the nanodroplets vaporized and loosened the tumor interstitium, facilitating drug penetration and accumulation into the tumor. Meanwhile, the released drug MPSU selectively accumulated in the endoplasmic reticulum, and after secondary ultrasound irradiation, a lot of ROS were generated in the endoplasmic reticulum. Thus, the endoplasmic reticulum stress pathway was activated, ICD was produced, and the maturation of DC cells is induced. Confocal experiments *in vitro* showed that the porphyrin fluorescence of PMPS NDs was distributed near the endoplasmic reticulum, while the porphyrin fluorescence of non-targeted group PPIX NDs was far away from the endoplasmic reticulum. These results suggested that PMPS can selectively accumulate into the endoplasmic reticulum with the aid of conjugate MPSU (Fig. 11).

The orthotopic pancreatic tumor model further confirmed the antitumor immunotherapy effect of SDT combined with αPD-L1. The weight of both primary and distant tumors in the experimental group was the lowest in all groups, and the number of $CD80^+CD86^+$ in peripancreatic, mesenteric, inguinal, and lumbar para-drainage lymph nodes (29.09 % ± 3.39 %) was significantly higher than that in other groups. Compared with the non-targeted group, the levels of IL-6 and TNF-α in serum in the targeted group were significantly increased.

In short, this cavitation assisted endoplasmic reticulum targeted synergistic therapy reflects a better tumor iSDT effect.

7.4.2. *Cell necroptosis*

Necroptosis is a type of programmed death that does not depend on the caspase pathway, and its activation mainly depends on the formation of necrotic bodies. Necrotic apoptosis causes a significant inflammatory response, manifested by the infiltration and activation of a mass of inflammatory cells, making dying cancer cells a stimulus for antitumor immune response. However, receptor-interacting protein kinase 3 (RIPK3), a key enzyme for necroptosis, is downregulated in most cancer cells, so the clinical translation of necroptosis is limited. To this end, Um et al. [162] reported a nanobubbles strategy that triggers RIPK3 independent necroptosis. Nanobubbles were synthesized by oil-in-water emulsion method using pegylated carboxymethyl dextran as hydrophilic skeleton, Ce6 as sonosensitizer and perfluoropentane as gas precursor. Under the action of exogenous ultrasound, cavitation effect is generated to promote cell membrane rupture, release damage related molecular patterns, and stimulate antitumor immunity in coordination

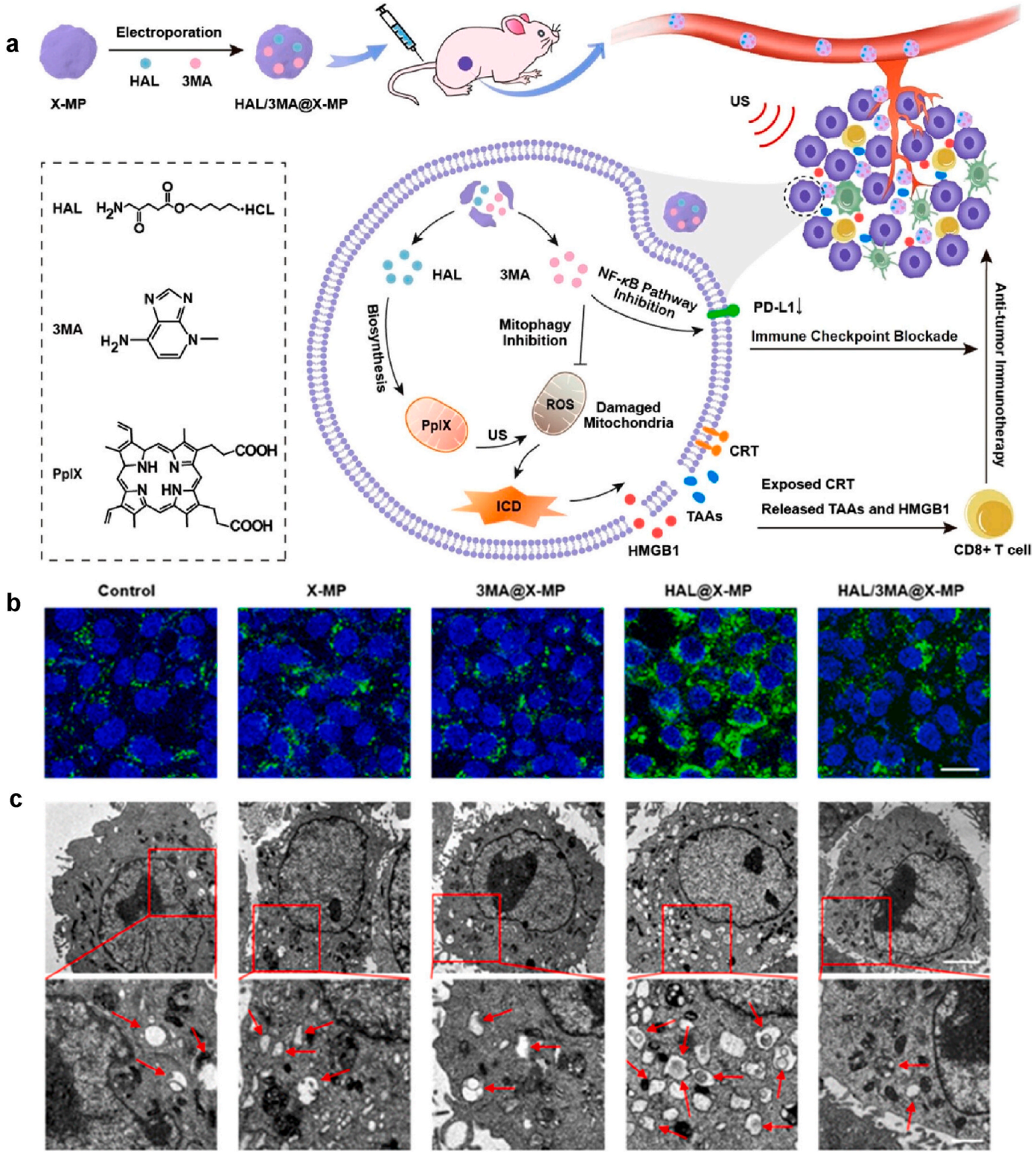


Fig. 14. Illustration of enhancing immunotherapy by autophagy in coordination with SDT. a) Scheme of the preparation and antitumor mechanism of HAL/3 MA@X-MP. b) CLSM and c) Bio-TEM images of autophagosomes in 4T1 cells after different treatments. Reprinted with permission from Ref. [166]. Copyright 2023, American Chemical Society.

with the SDT effect of Ce6. By confocal microscopy with annexin V/PI-stained cells, they clearly showed necroptosis characteristic cell membrane rupture and cytoplasmic swelling. A series of *in vitro* and *in vivo* experiments showed that NBs induced necroptosis promoted DCs maturation and CTLs invasion. The antitumor immune activity was significantly improved. The characteristic cell membrane rupture and cytoplasmic swelling of necroptosis were clearly revealed by confocal microscopy with annexin V/PI-staining. A series of *in vitro* and *in vivo* experiments had shown that NBs-induced necroptosis promoted the maturation of DCs and the infiltration of CTLs, significantly enhanced

the antitumor immune activity. Especially in RIPK3-deficient CT26 mouse models, the antitumor immune response against PD-L1 was amplified by NBs-mediated ICD, which not only completely regressed the primary tumor, but also significantly inhibited the growth of metastasis (Fig. 12).

In addition, immunostimulatory chemiluminescent resonance energy transfer nanoparticles (iCRET NPs) also had the effect of enhancing iSDT through the necroptosis pathway. This immuno-stimulated nanoparticle based on chemiluminescent resonance energy transfer (CRET) can produce CO_2 under ultrasound irradiation, which led to the typical cytoplasmic swelling of necroptosis and the rupture of cell membrane through the subsequent cavitation effect, releasing DAMPs such as HSP70 and HMGB1. The strong oxidation of biological substrates triggered by iCRET NPs under ultrasound, induced the occurrence of ICD, and in combination with αPD-L1, supplementing the function of effector T cells interfered with by immune checkpoint molecules, and thus exerting a synergistic effect. In 4T1 bearing mouse model, the antitumor immune response was significantly enhanced, and the tumor growth and metastasis were significantly inhibited [163] (Fig. 12).

7.4.3. Pyroptosis

Pyroptosis is another form of programmed death mode, which depends on the caspase pathway. Through specific GSDME protein cleavage mediated by caspase-3, the N-terminal domain is released, which binds to the cell membrane and punches holes, alters the cell osmotic pressure, and finally causes the cell to swell, lyse, and release pro-inflammatory cytokines such as IL-1β and IL-18, which activates the innate immune response. Therefore, precise control of pyroptosis is of great significance for tumor immunotherapy. At this time, ultrasound shows certain advantages due to its precise spatiotemporal control. On the basis of this theory, Chen et al. [164] used erythrocyte membrane to wrap PCN-224, a zirconium porphyrin porous coordination network, as a nanocarrier with the function of sonosensitizer to activate the pyroptosis pathway. However, since the extracellular matrix of most tumors is dense, which is not conducive to the infiltration of CTLs, they prepared LPM by simultaneously encapsulating TGF-β1 inhibitor LY364947 in nanocarriers to prevent the deposition of collagen and proliferation of fibroblasts, loose ECM, and promote the infiltration of CTLs. Experiments *in vitro* showed that cells treated with DAC (up-regulate GSDME) and LPM showed typical pyroptosis cell morphology under bright field optical microscopy after ultrasound irradiation. Western blot showed that the levels of caspase-3 and GSDME-N lysed under ultrasound irradiation in DAC + LPM group were significantly increased compared with other groups, further verifying the occurrence of pyroptosis. The levels of IL-1β and IL-18 in the experimental group were about seven times higher than in the other groups. Experiments *in vivo* showed that the tumor growth of 4T1 mice treated with DAC + LPM + US was significantly inhibited and almost completely disappeared. Tumor re-challenge model showed that LPM-mediated pyroptosis therapy significantly increase the central memory T cells (Tcm, about 5.4 times) and effector memory T cells (Tem, about 6.4 times) in spleen, and about 80 % of mice did not have re-tumor growth within 3 weeks, which once again proved that LMP-mediated pyroptosis therapy had excellent antitumor iSDT effect (Fig. 13).

7.4.4. Autophagy

Autophagy is a process of cell self-repair by removing abnormal cells to maintain normal cell function. It can be non-selective, such as macroautophagy and microautophagy, or selective, such as mitochondrial autophagy and endoplasmic reticulum autophagy, *etc*. For tumors, autophagy is a double-edged sword, on the one hand, it can protect tumor cells and reduce the damage of the surrounding environment to tumor cells, on the other hand, autophagy can inhibit tumor growth and metastasis at different stages of tumor development, and even initiate programmed death in some apoptosis-defective tumors. This characteristic of autophagy provides two distinct ideas for tumor therapy: inhibition of autophagy to improve the effect of antitumor therapy, or activation of autophagy to induce autophagic death of tumor cells. At present, inhibition of autophagy is still the mainstream of research.

SDT-induced tumor damage tends to activate the MAPK signaling pathway, producing cytoprotection and promoting cell survival by reducing apoptotic cells. Therefore, some scholars used chloroquine phosphate as the raw material to construct MChl-CQ-HP nanoparticle that co-delivered hemaporphyrin, surface engineered chlorescence and chloroquine phosphate, and maximized the iSDT effect of McHl-cq-hp-np on melanoma through SDT, local oxygenation and autophagy inhibition. The tumor reattack model further verified that this strategy had a strong immune memory effect [165].

Selective autophagy plays the role of house-cleaning under normal circumstances, such as depolarization of mitochondria in cells under external stimulation. The damaged mitochondria are specifically wrapped into autophagosomes and fused with lysosomes, thereby completing the degradation of mitochondria, and maintaining the stability of the intracellular environment. SDT of tumors mainly relies on ROS-induced mitochondrial damage, while mitochondrial autophagy neutralizes the SDT effect. To solve this problem, Zuo et al. [166] developed a bionic nanovesicle HAL/3MA@X-MP. Through the tumor homologous targeting ability of the nanovesicles, HAL and 3MA were co-delivered to tumor cells. Among them, hexyl 5-aminolevulinate hydrochloride (HAL) initiated the biosynthesis and local accumulation of PpIX in mitochondria through the heme synthesis pathway, and 3-methyladenine (3MA) acted as a mitochondrial autophagy inhibitor, which not only inhibited mitochondrial autophagy, but also downregulated the expression of PD-L1 through the NF-κB pathway, both of which produced ROS under the irradiation of exogenous ultrasound and induced severe damage to mitochondria. It also promoted the occurrence of ICD, blocked the recognition of immune checkpoints, effectively inhibited the growth of primary and distant tumor, the tumor inhibition rate exceeded 90 %. In addition, the survival period of mice was significantly prolonged, and no death occurred within 45 days (Fig. 14).

7.4.5. Ferroptosis

Ferroptosis is an iron-dependent mode of death that different from apoptosis, necrosis, and autophagy. It mainly catalyzes the lipid peroxidation of unsaturated fatty acids on cell membranes under the action of Fe^{2+} or ester oxygenase, thereby inducing cell death, which is mainly manifested by the reduction of GPX4, the core regulatory enzyme of the antioxidant system. Cao et al. [167] developed an oral nanohydrogel CS-ID@NMs that initiated ferroptosis while achieved SDT and CDT, accelerated the release of tumor antigens. They embedded mitochondrial-targeted indocyanine green derivatives (IDs) into hollow MnOx, modified their surfaces with regenerated silk fibroin (RSF) and chondroitin sulfate (CS), and finally coated them with chitosan/alginate hydrogel. After oral administration, the hydrogel passed through the gastrointestinal tract, CS-ID@NMs was released into the intestine. Driven by US and the produced O_2, the nanomotor crossed the mucus layer and was internalized by colon tumors through the specific binding of CS to CD44. In response to pH, GSH and ROS, the IDs encapsulated in the NMs were released and played the role of mitochondria targeted SDT. The released Mn^{2+} produced •OH and O_2 through the Fenton reaction, which enhanced the efficacy of SDT while induced CDT. All the above effects together lead to lipid peroxidation, induced ferroptosis and promoted the release of antigens. Under the action of αPD-L1, it further promotes the activation of T cells and enhanced the systemic antitumor immune response. To test the ability of this NMs to induce ferroptosis, they compared the activity of GPX4, the main regulator of ferroptosis, and the accumulation of LPO in different treatment groups. The results showed that CS-ID@NMs could effectively reduce the activity of GPX4. Under the additional irradiation of US, the activity of GPX4 was further decreased, and the green fluorescence representing lipid peroxidation was the strongest in CS-ID@NMs + US group. These results indicated that CS-ID@NMs induced more lipid peroxidation through SDT, CDT

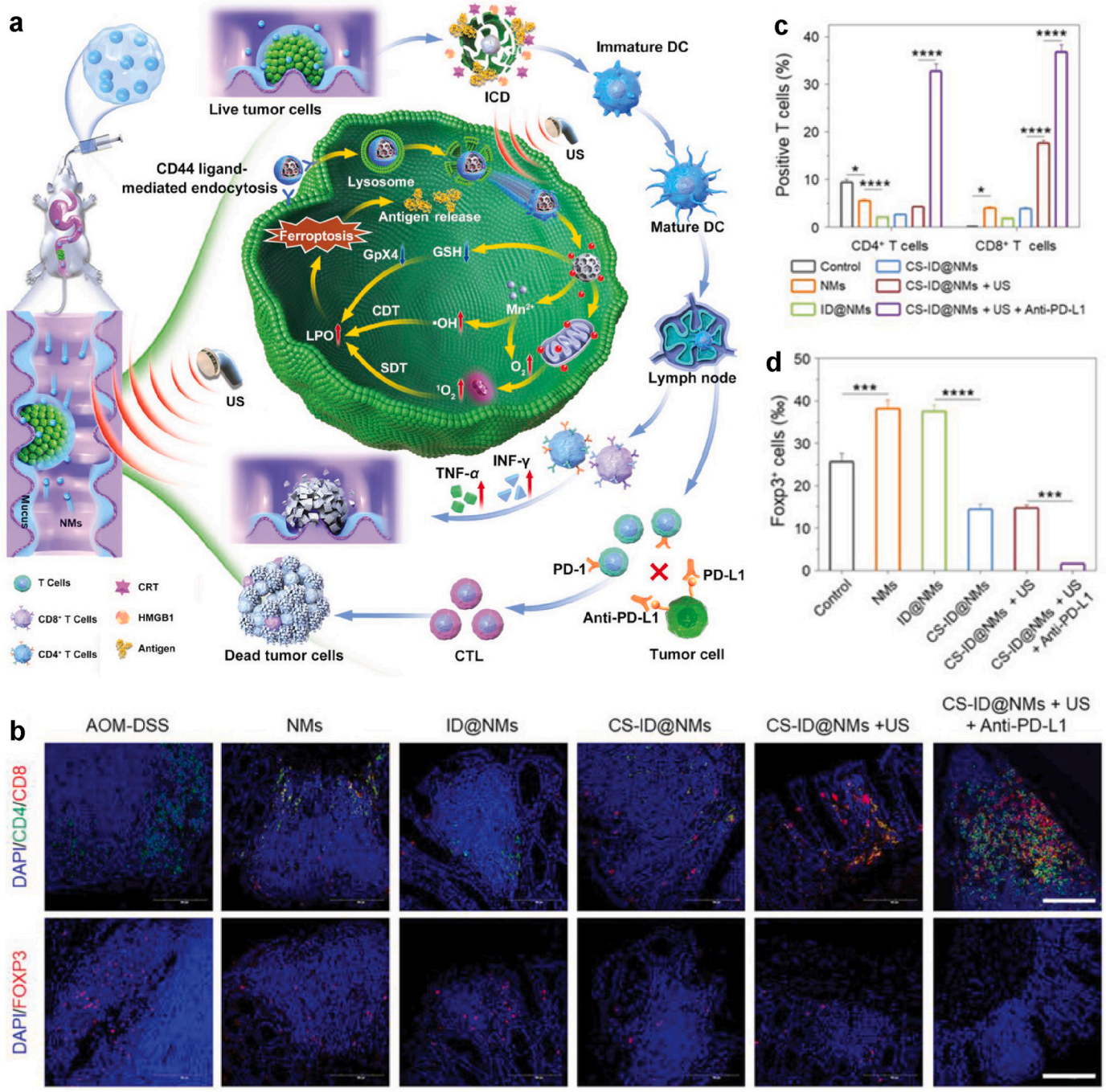


Fig. 15. Illustration of enhancing immunotherapy by Ferroptosis in coordination with SDT. a) Scheme of CS-ID@NMs as multi-functional motors achieved efficient mucus-traversing ability, deep tumor penetration and potentiation of antitumor immunity. b) Immunofluorescence staining of $CD4^+$ $CD8^+$ T cells, $Foxp3^+$ cells and quantitative analysis of c) $CD4^+$ $CD8^+$ T cells and d) $Foxp3^+$ cells in the tumors after various treatments. Reprinted with permission from Ref. [167]. Copyright 2022, Wiley-VCH.

and the consumption of GSH, thereby activating the ferroptosis pathway, rapidly leading to cell death, and releasing lots of DAMPs, resulting in the occurrence of ICD (Fig. 15).

7.4.6. Gas therapy

As a safe and effective treatment modality, gas therapy has attracted extensive concern as a way to enhance the efficacy of SDT [168]. These gases with special therapeutic effects include H_2S, CO_2, O_2, NO, CO, *etc.*, each of which has a different antitumor mechanism. For example, H_2S in higher concentration destroys the mitochondrial electron transport chain by inhibiting cytochrome C oxidase and promotes oxidative stress and DNA damage. In addition, it can reduce the accumulation of immunosuppressive cells in tumors, induce the maturation of DCs, and increase the infiltration of CTLs. Based on this, Li et al. [169] prepared titanium sulfide nanosheets (TiS_x NSs) as H_2S donors. With the release of H_2S, nanosheets were gradually oxidized to TiO_x, becoming a good sonosensitizer, and generating ROS under ultrasound. This cascade biological effect can inhibit mitochondrial respiration and ATP synthesis, lead to apoptosis of cancer cells, induce the maturation of DCs, and thus initiate antitumor immune response. The mouse model of 4T1 showed that the growth of primary tumors in the TiS_x + US group was completely inhibited, while the tumor inhibition rate in the group

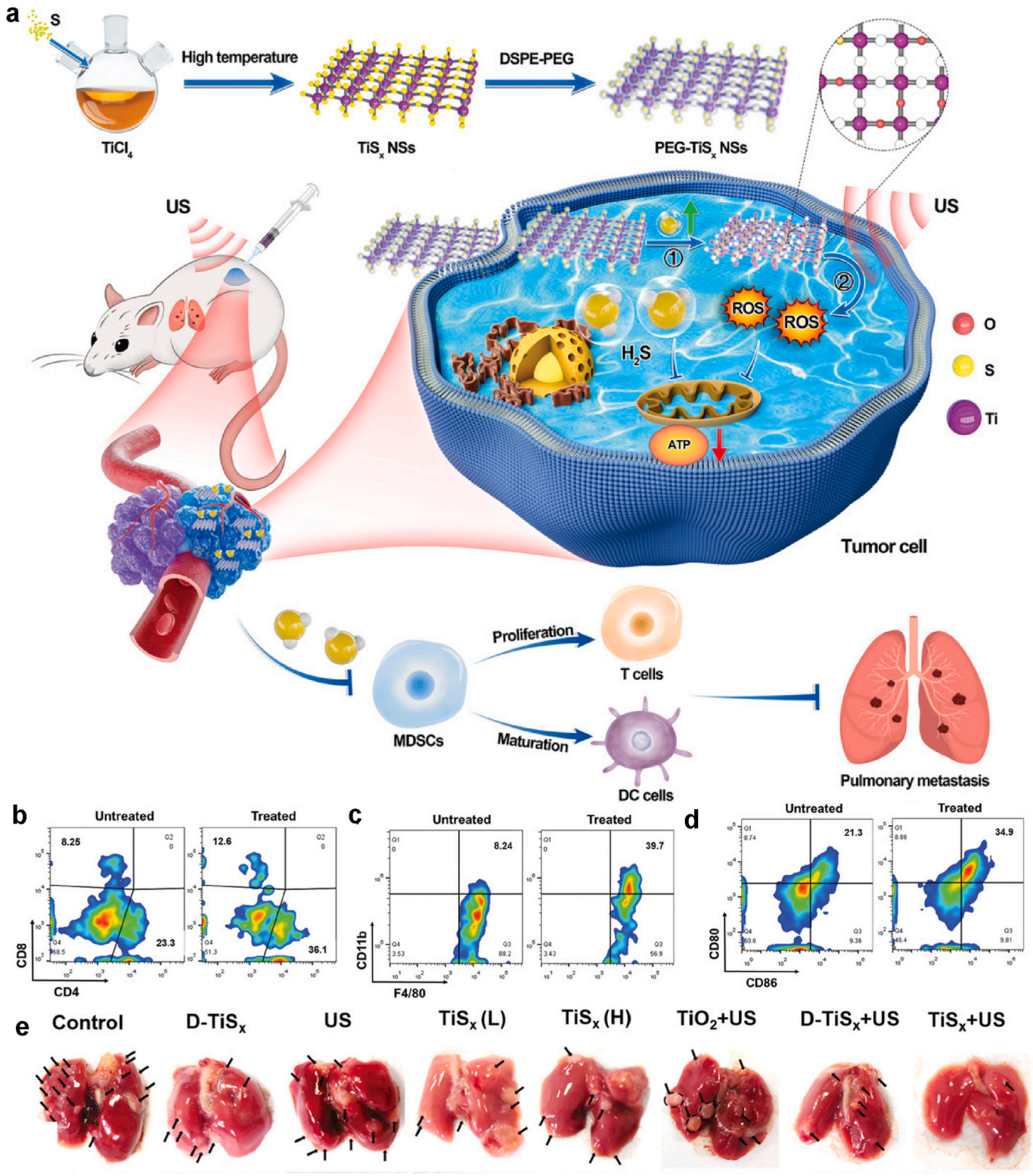


Fig. 16. Illustration of enhancing immunotherapy by gas therapy in coordination with SDT. a) Scheme of TiS_x NSs as bioreactors to enhance antitumor immunotherapy. Flow cytometry results of b) $CD4^+$ T cells, c) M1 macrophages in tumors after treated with TiS_x NSs. d) Flow cytometry results of mature DCs in lymph nodes after treated with TiS_x NSs. e) Digital photographs of lung metastases in different groups. Reprinted with permission from Ref. [169]. Copyright 2022, Wiley-VCH.

without US irradiation was only about 46.7 %, and lung metastases were also significantly reduced. Subsequent analysis showed that the experimental group showed obvious inhibition of MDSCs, the content of mature DCs in the DLNs increased significantly, and the levels of M1-related cytokines IL-6, IL-12 and TNF-α also increased significantly, further proving the synergistic effect of gas therapy and SDT on the activation of the immune system (Fig. 16).

O_2 provides the necessary source of gas molecules for SDT, and they help inhibit tumor growth and metastases caused by hypoxia. As an endogenous gas transmitter, NO will directly damage mitochondria at

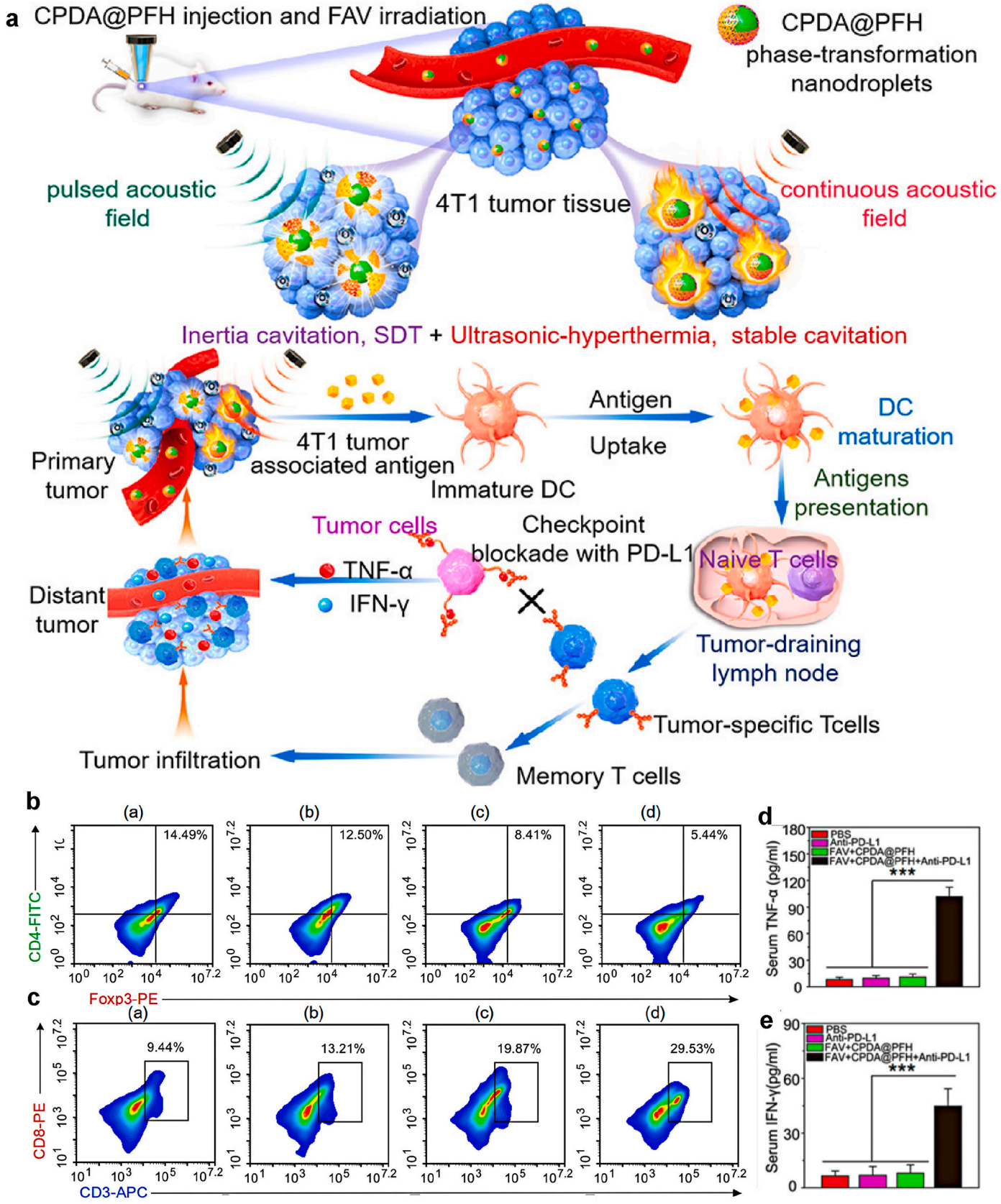


Fig. 17. Illustration of enhancing immunotherapy by all-in-one strategy. a) Mechanism of CPDA@PFH regulated by Focused Acoustic Vortex to enhance antitumor immunotherapy. Flow cytometry plots of b) $CD4^+$ $Foxp3^+$ T cells in distant tumor and c) $CD3e^+$ $CD8^+$ T cells in primary tumor 7 days after various treatments. The level of d) TNF-α and e) IFN-γ detected by ELISA 7 days after various treatments. Reprinted with permission from Ref. [172]. Copyright 2022, American Chemical Society.

high concentrations, indirectly alleviate tumor hypoxia by inhibiting mitochondrial respiration, improve the efficacy of SDT, and react with ROS produced by SDT to generate more toxic peroxynitrites ($ONOO^-$) and other active nitrogen (RNS), further improve the tumor cell killing effect. Thus, Ji et al. [170] reported a system for encapsulating perfluorodecalin (PDC) and mitochondria targeted sonosensitizer IR780 with a human serum albumin based NO donor. After PIH-NO accumulated in mitochondria, it was irradiated with ultrasound to release O_2 and NO at the same time, and produce ROS, $ONOO^-$ and RNS, leading to mitochondrial dysfunction and apoptosis. NO can also induce the expression of angiogenic factors, thereby promoting the normalization of tumor blood vessels, improving hemoperfusion of tumors, further promoting the accumulation of nanoparticles, so as to continuously enhance the efficacy of SDT, inhibit tumor growth, amplify ICD, promote the maturation of DCs and the infiltration of CTLs. In addition, PIH-NO can also realize the repolarization of macrophages, increase the content of M1 macrophages, deplete immunosuppressive cells such as MDSCs and Tregs, and enhance the immune response.

In another study [171] more skillfully combined SDT, NO gas therapy with chemotherapy, they prepared nanodroplets that co-delivered paclitaxel and L-arginine (L-Arg) by homogenization/emulsification method. The bubbles generated by L-Arg@PTX nanodroplets under ultrasound can greatly promote the release and accumulation of sonosensitizers in deep tissues, and the cavitation effect can reduce the cavitation threshold intensity of SDT. ROS produced by SDT oxidized L-Arg to produce NO. In this case, SDT and NO had a synergistic effect with paclitaxel to achieve a powerful tumor suppressive effect in Hepa1-6 tumor bearing mouse models. Immunofluorescence staining of tumor sections showed that CRT expression on cell membranes of L-Arg@PTX NDs + US group was significantly increased, and flow cytometry showed that the percentage of $CD3^+CD8^+$ cells in this group was significantly higher than that in other groups (18.6 ± 1.5 %), and serum levels of IFN-γ and TNF-α were also significantly increased. These results further verified that SDT, NO and chemotherapy co-induced ICD, promoted the maturation of DC cells, and increased infiltration of $CD8^+$ CTLs to activate the synergistic effect of anti-tumor immune response.

All in all, gas therapy, as a green therapy, safely and effectively promotes the effect of sonodynamic immunotherapy, and their reasonable combined use will have broad application prospects.

7.4.7. *All-in-one strategy*

Due to tumor heterogeneity and immunosuppressive nature of TME, it is difficult for a single therapy to achieve complete tumor elimination. In recent years, with the emergence of various treatments and concepts, the combination strategy of multiple therapies has shown greater advantages. For example, Wu et al. [172] constructed an all-in-one strategy based on focused acoustic vortex modulated composite nanodroplets CPDA@PFH, and combined with ICIs to achieve hyperthermia-cavitation-SDT-immunotherapy cascade amplification synergistic therapy. This combined strategy effectively inhibited the growth of primary tumor and distal tumor in 4T1 mouse models (98.41 % and 80.71 %), reduced the number and volume of lung metastases. Under the effect of immune memory, the survival rate of 4T1 bearing mice was as high as 57.14 % after 60 days of treatment (Fig. 17).

In another example, a strategy of encapsulating Ru–TePt and PD-L1 siRNA by biomimetic cell membrane vesicles expressing transferin realized the multifunctional integration of CDT-SDT-gene therapy-immunotherapy, which effectively induced the activation of adaptive immunity [173]. Ru–TePt acted as a charge trap to hinder the recombination of electron-hole (e^--h^+), generated •OH and $^1O_2$, and enhance the efficiency of SDT. Ru–TePt achieved oxygen production in-situ in the process of generating •OH by reacting with H_2O_2 rich in the tumor, reduced SDT resistance caused by hypoxic TME, amplified the effect of SDT, induced ICD, and released more DAMPs to participate in the occurrence of adaptive immunity. At the same time, due to the targeting of biomimetic cell membrane vesicles, the gene silencing ability of PD-L1 siRNA was improved, which further amplifying the immune activation effect.

In general, scholars have tried to integrate various cancer therapies with SDT through multiple strategies to induce powerful ICD and activate a systemic immune response. At present, gratifying achievements have been made in various preclinical studies. How to achieve better clinical transformation will be the focus and difficulty of the further research.

8. iSPT for cancer

The piezoelectric effect is a phenomenon in which a medium deforms under the action of mechanical stress to produce electron polarization, or conversely, when an electric field is applied along the direction of polarization, the medium deforms. Among them, the build-in electronic field generated by electron polarization caused by deformation promote cell apoptosis, which plays an extremely important role in tumor therapy [174,175]. As an exogenous stimulus, ultrasound has the advantage of deep tissue penetration. The mechanical stress generated by ultrasound activates the piezoelectric effect, transmits the electrical stimulus to the target tissue wirelessly and accurately, drives the chemical reaction through piezoelectric catalysis, generates ROS, mediates the intracellular redox reaction, and achieves the purpose of tumor treatment [176–179]. This approach is called SPT.

In recent years, scholars have found that SPT is able to activate ICD [180] or regulate the polarization of macrophages [181], trigger systemic antitumor immune response, and play the role of iSPT.

Chitosan-exfoliated monolayer MoS_2 (Ch-Ms) self-assemblies with Ti_3C_2 to form Ti_3C_2-chitosan -MoS_2 (TC@Ch-Ms), under the mechanical deformation caused by US or NIR light, the surface of MoS_2 generated an unbalanced charge and splits the surrounding water to produce O_2 and •OH. Metal-semiconductor contact with schottky modal and piezoelectric excitation of unbalanced charges further promote the reduction of molecular oxygen to superoxide anion ($•O_2^-$), or promote the reduction of hydrogen peroxide to •OH, thus activating ICD [180]. Experiments *in vitro* showed that 4T1 cells secreted a large amount of ATP into the medium 3 h after TC@Ch-MS + US + NIR treatment, and the average fluorescence intensity of CRT on the plasma membrane increased significantly 12 h after treatment. HMGB1 was highly expressed in the cytoplasm of TC@Ch-MS + US + NIR group, while HMGB1 was limited to the nucleus of the control group. The 4T1 tumor bearing mouse model showed that HMGB1 migrated to cytoplasm 24 h after treatment, which was consistent with the results of *in vitro* experiments. At this time, there were no significant changes in immune cells in the DLNs, while the DCs and $CD8^+$ T cells in the TC@Ch-MS + US + NIR group (18.2 % and 40.5 %) were significantly higher than those in the control group (5.89 % and 20.7 %). 20 days after treatment, most of the tumors in TC@Ch-MS + US + NIR group disappeared and complete remission was achieved, and the number of $CD8^+$ T cells in lymph nodes, especially effector $CD8^+$ T ($CD44^+CD62L^-$) cells, were significantly increased compared with the control group.

Another mechanism is that the micro-vibration of the piezoelectric material is driven by ultrasound, and the Ca^{2+} influx is triggered by the fluctuation of ion current to affect the potential, and the selective expression and secretion of pro-inflammatory factors are triggered through the Ca^{2+}-CAMK2A–NF–κB axis, and macrophages are repolarized [181]. Kong et al. used β-phase poly (vinylidene fluoride) (β-PVDF) film with all-trans conformation and net dipole moment as piezoelectric material, which caused film deformation through ultrasound irradiation. Ca^{2+} promoted the release of TNF-α, IL-1β and monocyte chemotactic protein 1 (MCP-1) through voltage-gated channels and Ca^{2+}-CAMK2A–NF–κB axis, enhanced the polarization of M1, inhibited the polarization of M2, and exerted tumor killing effect.

Due to the impenetrability of conventional chemotherapy drugs in solid tumors, and the immunosuppressive effect of lactic acid produced by tumor metabolism, Wu et al. [182] proposed a new strategy of

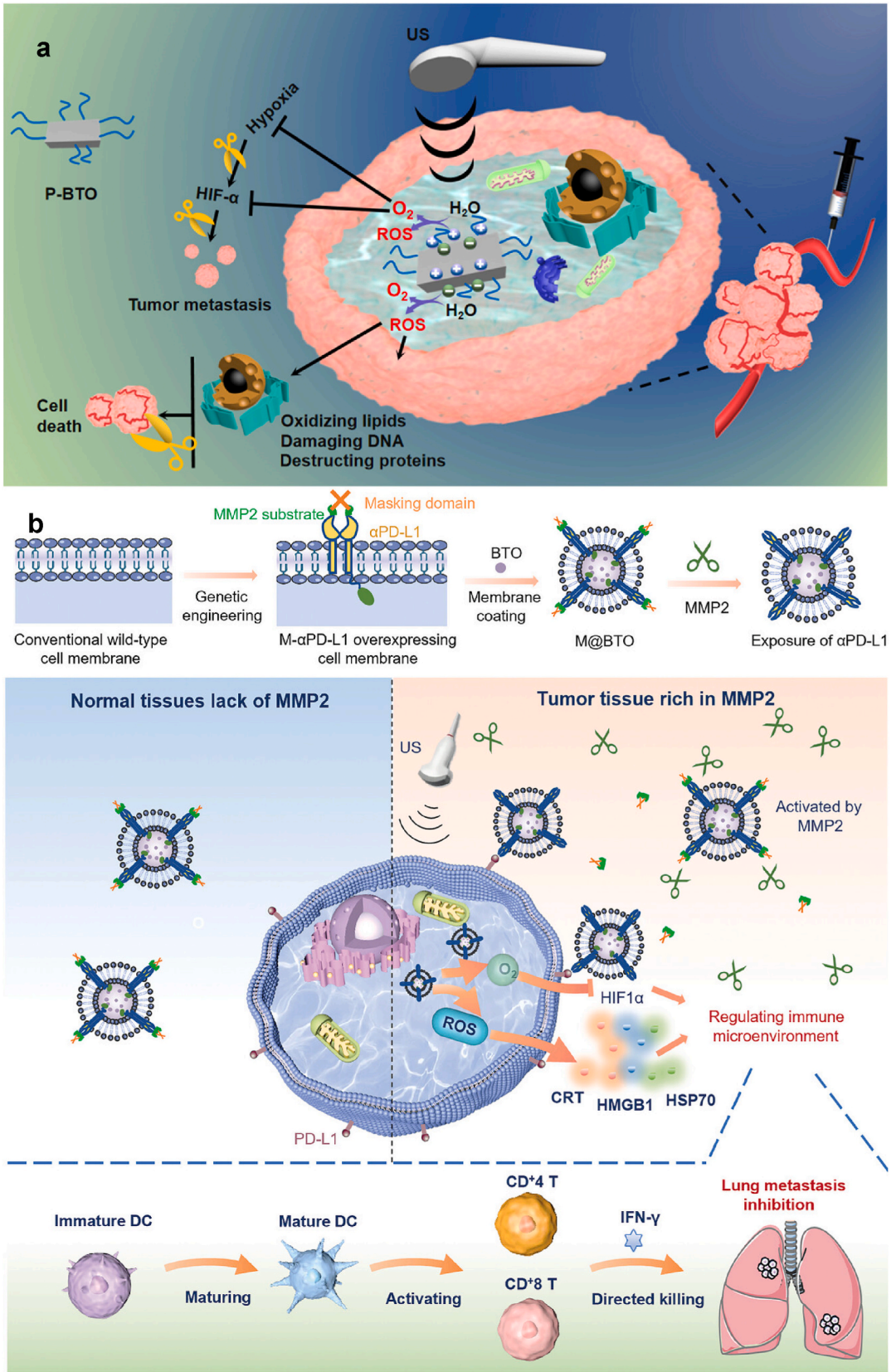


Fig. 18. Illustration of enhancing immunotherapy by SPT. a) illustration of the mechanism of sonopiezoelectric therapy. Reproduced with permission from Ref. [176]. Copyright 2021, American Chemical Society. b) Piezoelectric catalysis for enhanced immunotherapy. Schematic depiction of M@BTO mediated iSPT. Reproduced with permission from Ref. [183]. Copyright 2023, Wiley-VCH.

Table 1
Different nanomaterials and US bioeffects for cancer immunotherapy.

Therapy	Integration strategies	Immune targets	Tumor models	Ref.
iSTT	FUS + GEM + αPD-1	MDSC	4T1 breast cancer	[107]
iSTT	PLGA-R837/PLGA-MPLA + HIFU + αCTLA-4	TLR7/TLR4, CTLA-4	CT26 colorectal cancer	[108]
iSTT	M@SOP + HIFU	DC, T cell ($CD8^+$), TAM	4T1 breast cancer	[111]
iSTT	MBP + HIFU	DC, T cell ($CD4^+$, $CD8^+$)	4T1 breast cancer	[112]
iSMT	MBs + LIFU-TMD	DC, T cell ($CD8^+$)	4T1 breast cancer	[123]
iSMT	USMC + αPD-L1	T cell ($CD8^+$)	MC38 colon cancer	[124]
iSMT	TMB + pDNA + LFUS + αPD-L1	T cell ($CD8^+$), macrophages	NDL breast cancer	[130]
iSMT	CLMBs-loaded sPD-1 and miR-34a + UTMD	CTL	U14 cervical cancer	[131]
iSMT	αPCF-MB + US	CTL	CT26 colon cancer	[133]
iSMT	RD@MBs + UTMD + αPD-L1	T cell, TAM, MDSCs	4T1 breast cancer, CT26 colon cancer	[132]
iSMT	GVs + FUS + αCTLA-4 + αPD-L1	CTLA-4, PD-1/PD-L1	A20 lymphoma	[135]
iSMT	UN +αPD-L1	DC, T cell ($CD8^+$)	MC38 colon cancer	[138]
iSDT	SPN_{Ab} + US	CTL, Treg, CTLA-4	4T1 breast cancer	[146]
iSDT	$TiSe_2$ + US +αPD-1	DC, T cell ($CD8^+$), Treg	Panc02 pancreatic cancer	[143]
iSDT	P-αPD-L1/C + US	T cell	B16–F10 melanoma	[144]
iSDT	HMME/R837@Lip + US + αPD-L1	TLR7, DC, T cell ($CD8^+$)	4T1 breast cancer, CT26 colorectal cancer	[13]
iSDT	MRP + US +αPD-L1	TLR7, DC, T cell, TAM	CT26 colorectal cancer	[150]
iSDT	HMME@BiL + US + SR717	T cell ($CD8^+$), NK cell	CT26 colorectal cancer	[148]
iSDT	PSPA + US	T cell	4T1 breast cancer	[149]
iSDT	PEG-b-Pho + US + αPD-L1	DC, CTL	4T1 breast cancer	[151]
iSDT	Lipo-ce6/TPZ@MH + US	DC, T cell ($CD8^+$)	B16–F10 melanoma	[153]
iSDT	SPNTi + US	MDSCs	4T1 breast cancer	[154]
iSDT	PgP@Fe–COF + US + αPD-L1	DC, T cell	4T1 breast cancer	[155]
iSDT	TIR@siRNA + US + ^{D}PPA-1 peptide	T cell	CT26 colorectal cancer	[145]
iSDT	MPIRx + US	TAM, CD47	Osteosarcoma	[156]
iSDT	M-H@lip-ZA + US	TAM, T cell ($CD8^+$)	4T1 breast cancer	[158]
iSDT	NCG + US + αPD-L1	MDSC, TAM, T cell	CT26 colorectal cancer	[157]
iSDT	NP_{MCA} + US	DC, T cell ($CD4^+$, $CD8^+$)	4T1 breast cancer	[152]
iSDT	Zr-TCPP(TPP)/R837@M + US + αCTLA-4	TLR7, DC, T cell ($CD8^+$)	4T1 breast cancer	[160]
iSDT	PMPS NDs + US + αPD-L1	DC, T cell ($CD8^+$), NK cell	Pancreatic cancer	[161]
iSDT	PFP@PEG-CMD-Ce6 + US + αPD-L1	DC, T cell ($CD8^+$)	RIPK3-deficient, CT26 colorectal cancer	[162]
iSDT	iCRET + US + αPD-1	DC, T cell	4T1 breast cancer	[163]
iSDT	LPM + US + DAC	DC, T cell ($CD8^+$)	4T1 breast cancer	[164]
iSDT	MChl-CQ-HP-NP + US	CTL, NK cell, T cell ($CD8^+$)	B16 melanoma	[165]
iSDT	HAL/3MA@X-MP + US	DC, T cell	4T1 breast cancer	[166]
iSDT	CS-ID@NM/hydrogel + US + αPD-L1	DC, T cell	CT26 colorectal cancer	[167]
iSDT	TiSx NSs + US	DC, T cell, MDSC	4T1 breast cancer	[169]
iSDT	PIH-NO + US	DC, TAM, MDSC	4T1 breast cancer	[170]
iSDT	L-Arg@PTX + US	T cell ($CD8^+$)	Hepa1-6 hepatocellular carcinoma	[171]
iSDT	CPDA@PFH + FAV + αPD-L1	DC, T cell	4T1 breast cancer	[172]
iSDT	Ru–TePt@siRNA-MVs + US	DC, T cell	B16–F10 melanoma	[173]
iSPT	TC@Ch-MS + NIR + US	DC, T cell ($CD8^+$)	4T1 breast cancer	[180]
iSPT	B-PVDF + US	TAM	4T1 breast cancer	[181]
iSPT	SSN + US	T cell ($CD8^+$, Treg)	Hepa1-6 hepatocellular carcinoma	[182]
iSPT	M@BTO + US + αPD-L1	CTL	B16–F10 melanoma	[183]

MBs: microbubbles; LIFU-TMD: low intensity focused ultrasound-targeted microbubble destruction; USMC: ultrasound stimulated microbubble cavitation; TMB: targeted microbubbles; LFUS: low frequency US; CLMBs: cationic lipid microbubbles; FAV: Focused acoustic vortex.

immune activation in response to ultrasound piezoelectric SnS nanoplates (SSN), which can efficiently treat deep tumors by piezoelectricity catalyzing H_2 production and LA deprivation. The PD-L1 overexpression was down-regulated by respiratory suppression and energy regulation by the piezoelectric generation of H_2 by SSN, which liberated effector $CD8^+$ T cells from the immunosuppression of tumor cells, while LA deprivation synergistically activated antitumor immunity through the $CD8^+$ T/Tregs pathway. The orthotopic liver cancer model showed that tumors were completely eradicated and 100 % of tumor bearing mice survived. This ultrasound driven piezoelectric catalyzed tumor immune activation strategy opened up a safe and effective approach for the treatment of deep tumors.

Tang et al. [183] utilized ROS and O_2 produced by piezoelectric catalysis and H_2O decomposition to promote intratumoral invasion of CTLs through ROS-mediated ICD independent of TME, thus improving PD-L1 blockade therapy. Moreover, genetically engineered cell membrane coated with barium titanate nanoparticles were cleverly used to cut the MMP-2 substrate on the membrane through the MMP-2 enzyme rich in tumor cells, achieving selective detachment of the masking domain to expose PD-L1 antibody. While enhancing the immune response, the PD-1/PD-L1 cascade reaction at the tumor site was specifically blocked, the immunosuppressive microenvironment of the tumor was overcome, and the "immune-cold" tumors were transformed into "immune-hot" tumors, so as to play the role of antitumor immunotherapy. The results of B16F10 cell experiment showed that M@BTO + MMP2 + US was superior to other groups in inducing CRT exposure, HMGB1 release and HSP70 expression. In the melanoma bearing mouse model, the percentage of mature DCs in DLNs in M@BTO + US group was as high as 31.8 %, which was significantly higher than 7.65 % in PBS group, 10.1 % in free αPD-L1 group and 14.5 % in M@BTO NPs group. The expression level of Granzyme B in the experimental group was also significantly increased, up to 53.4 %, which was higher than 20.8 % in the PBS group, 34 % in the free αPD-L1 group and 43.1 % in the M@BTO NPs group, indicating that M@BTO could effectively activate the antitumor immune response under the action of ultrasound. The reduced number of lung metastases further verified that this strategy can effectively inhibit tumor growth and lung metastasis (Fig. 18).

In summary, although some progress has been made in the field of iSPT in the past few years, this field is still in the infant stage, facing many opportunities and challenges, and needs to be further developed and improved.

9. Conclusions and future perspectives

In recent years, with the in-depth research of the biological effects of ultrasound, immunotherapy and nanomaterials, various ultrasound mediated tumor immunotherapy strategies have been developed to overcome the shortcomings confronted by immunotherapy, such as low response rate and severe immune-related adverse events. In this paper, we reviewed the latest progress in enhancing immunotherapy with various ultrasound biological effects, including sonothermal effects, sonomechanical effects, and sonochemical effects according to different biological mechanisms, and highlights the important role of nanomaterials in the process of strategy integration. Table 1 summarizes the different nanomaterials and US bioeffects for cancer immunotherapy. This multidisciplinary integration strategy effectively activates the immune system in the tumor model, generate antitumor immune response and immune memory effect, eliminate the primary tumor, inhibit the occurrence of distant metastasis and prevent the recurrence of tumor.

Although significant progress has been made in this field, it is still limited to animal experiments and preclinical studies currently, and there is still a long way to go before the real clinical translation, among which there are many key issues to be solved.

The first is the biosecurity of the combination strategy, which is a top priority. Before a new treatment enters the clinic, it is necessary to ensure its safety, whether it is short-term biosafety or long-term biological effects, which is crucial for cancer patients. The current experimental results usually evaluate the short-term biocompatibility, cycle stability and off-target toxicity of nanomaterials, and most of the experimental data come from animals. Therefore, the long-term biological effects of these innovative materials on human populations should become the primary problem to be solved in clinical translation. In addition, the setting of parameters in the process of sonotherapy also needs to consider the issue of safety, as an emerging research content, there is no unified standard at present, and experts from various countries need to work together to form a relatively consistent standard.

Secondly, ultrasound bioeffects mediated immunotherapy relies on exogenous ultrasound stimulation, and the main strength of ultrasonic instrument research and development at this stage is still concentrated on clinical diagnostic system, rather than tumor immunotherapy targeted at ultrasonic response. As an emerging field, it lacks standard or professional ultrasound instruments and equipments to obtain efficient, stable and homogeneous treatment results. Therefore, in order to accelerate the clinical translation of ultrasound mediated cancer immunotherapy strategy, it is necessary to clarify the mechanism of ultrasound-mediated bioeffects of immunotherapy, and develop corresponding ultrasonic equipments on this basis, so as to achieve the standardization of exogenous stimulation and better promote the realization of clinical translation.

Finally, nanomaterials, as carriers for ultrasound mediated cancer immunotherapy, play a pivotal role in the process of functional realization. To achieve its clinical translation, it is necessary to ensure that nanomaterials integrate functions under simple designs to achieve efficacy that is superior to a single method. Only in this way, large scale and reproducible production can be achieved, and this homogeneous production is an important factor in the clinical translation of this therapy.

All in all, in order to promote the development of ultrasound mediated cancer immunotherapy, we should devote more efforts to the above key issues, promote the real clinical translation of this emerging field in the near future, and provide more choices for cancer patients to benefit human health.

CRediT authorship contribution statement

Xinxin Xie: Investigation, Writing - original draft, Writing - review & editing. **Jinxia Zhang:** Writing - review & editing. **Yuan Wang:** Writing - review & editing. **Wanrui Shi:** Validation. **Rui Tang:** Resources. **Qingshuang Tang:** Resources. **Suhui Sun:** Resources. **Ruiqi Wu:** Resources. **Shuyu Xu:** Validation. **Mengxin Wang:** Validation. **Xiaolong Liang:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing - review & editing. **Ligang Cui:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing - review & editing.

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

Data will be made available on request.

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