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Research progress on new physical therapies for cancer (Review)

JINGYI XI[1,2*], CHENG JI[3*], HAIXIN SUN[1,2], YURUN WU[1,2], CHENGJIE SHI[3], SHASHA LI[1,2], TAO YANG[1,2], YUXIANG SHEN[3], YULIN LI[1,2], YAOXUAN FAN[1,2], QICHAO ZHAO[1,2], SHUIPING LIU[1,2], TIAN XIE[1,2] and GONGXING CHEN[1,2]

[1]Department of Pharmacy Experiment, School of Pharmacy, Hangzhou Normal University, Hangzhou, Zhejiang 311121, P.R. China; [2]Key Laboratory of Elemene Class Anti-Cancer Chinese Medicines, Engineering Laboratory of Development and Application of Traditional Chinese Medicines, Collaborative Innovation Center of Traditional Chinese Medicines of Zhejiang Province, Hangzhou Normal University, Hangzhou, Zhejiang 311121, P.R. China; [3]Department of Medicine, Hangzhou Normal University, Hangzhou, Zhejiang 311121, P.R. China

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Abstract. Currently, the clinical treatment of cancer is mainly based on surgery, chemotherapy and radiotherapy, but there are still problems associated with these treatments, such as disease recurrence and adverse reactions. The complexity and harmful nature of cancer mean that combining multiple treatment methods is an inevitable response. Therefore, it is of theoretical and practical significance to expand upon and study the aforementioned classic and traditional measures. With the advancement of technology, physical therapy has become important in the current research and treatment of cancer, and the physical factors related to cancer deserve in-depth study and discussion. The present review aimed to describe the mechanisms of action of pressure, temperature, photo-, sound and other physical therapies for cancer, which may provide new avenues for cancer treatment.

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Correspondence to: Dr Gongxing Chen, Department of Pharmacy Experiment, School of Pharmacy, Hangzhou Normal University, 2318 Yuhangtang Road, Hangzhou, Zhejiang 311121, P.R. China
E-mail: 20070002@hznu.edu.cn

*Contributed equally

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1. Introduction

Although cancer treatment has made great progress, it is a major cause of morbidity and mortality worldwide (1,2). According to data from the Global Cancer Report, ~19.3 million new cancer cases and ~10 million cancer death cases occurred worldwide in 2020, including ~4.57 million new cancer cases and ~3 million cancer deaths in China alone (3).

With improvements in medical treatments, traditional cancer therapies, such as surgery, chemotherapy and radiotherapy, have evolved. Although these treatments can inhibit the growth of tumor cells, there are certain harmful effects on normal cells (4-7). Due to the heterogeneity of cancer, gene mutations of different cancer cells in patients with the same type of tumor are not necessarily the same, resulting in increased difficulties in cancer treatment (8). Drugs that improve cancer treatment effects and reverse drug resistance have become the focal point in the current research on drug-resistant tumors (9-14). However, due to the interactions between different drugs, the efficacy of combination therapy remains suboptimal in clinical practice (15) and there are still adverse reactions caused by chemotherapy (16). Therefore, it is necessary to perform further research to develop safe and effective cancer treatments.

The tumor microenvironment (TME) refers to the surrounding microenvironment in which tumor cells exist, including surrounding blood vessels, immune cells, cancer-associated fibroblasts, myeloid-derived suppressor cells, signaling molecules and the extracellular matrix (Fig. 1) (17). The interaction between tumor cells and the microenvironment can be a molecular target for tumor therapy. The cellular and molecular composition corresponding to the TME and the chemical and physical factors involved in tumor growth have attracted increased research interest. Multiple studies have confirmed that the TME's cellular and molecular composition affects tumor cell growth, invasion and metastasis (18-21).

Immunotherapy is a novel cancer therapy method (22). Immune cells in the immune system, such as natural killer (NK) cells, serve an important role in tumor immunotherapy and interact with the TME to inhibit the growth of tumor cells (Fig. 1) (23). A number of studies have focused on genetic and biochemical factors as the causes of malignant tumors (20,21). However, physical factors in the TME have not been widely studied (24). Tumor cells are typically confined to specific microenvironments and changes in physical factors in the TME will also affect the behavior of tumor cells, such as solid stresses generated by tumor growth (25). Therefore, the changing characteristics of physical factors in the microenvironment also serve a key role in tumor development.

Physical therapy for tumors, by changing the living environment of tumor cells through physical means, may become a new and effective treatment strategy that can be used to treat most types of tumor diseases. The present review aimed to summarize the mechanisms of application of physical stimuli such as pressure, temperature, light, sound and other therapies, in tumor treatment, to provide a basis for new treatments and research on tumors.

2. Pressure

Over the past decades, studies have reported the critical role of mechanics in the TME (26,27). Cells in tissues such as the heart, lung and skeleton encounter nanoscale to macroscale forces that are integral to their function, such as the shear stress induced by blood flow on a vessel wall (Fig. 1) (28). Cancer cells have been reported to be fibrosis of normal cells; the cellular architecture in tumors is severely altered and is typically characterized by a stiffened extracellular matrix (29). Cells can sense exogenous forces through mechanical transduction and transform them into biological signals (30). The TME affects the growth of tumor cells through physical and chemical stimulation (31) and responds to changes the tumor cells in the TME. Mechanical factors include contractile force, shear stress, hydrostatic pressure, intercellular tension and extracellular matrix stiffness. Changes in mechanical factors in the TME can affect tumor transformation, invasion and metastasis (32). Therefore, the study of tumor mechanics may be a future direction for developing tumor-targeted drugs. When analyzing the force on cells from a microscopic perspective, the cells are affected by two sets of balancing forces: Gravity and supporting force; the swelling pushing force of osmotic pressure on the cell membrane and the pulling force of the cytoskeleton pulling the cell membrane inward (Fig. 1). Gravity and support are weak and negligible. The balance between the swelling force of osmotic pressure and the pulling force of the cytoskeleton is a basis for cell survival. If this mechanical balance is destroyed, changes in the cellular microenvironment occur, affecting the biological function of the cell, including tumor cells. Pressure therapy can be divided into high-pressure therapy (HHP) and negative-pressure therapy (NP). HHP induces immunogenic cell death (ICD) in tumor cells and shows broad prospects in developing tumor vaccines and enhancing tumor cell sensitivity. NP uses the defects in the osmotic pressure regulation ability of tumor cells to rupture the cell membrane by reducing the external pressure environment, thereby selectively killing tumor cells without damaging normal cells.

HHP. HHP was first used to inactivate microorganisms in milk (33). It can damage microbial cell membranes and cell walls, change the cell morphology, affect intracellular enzyme activity and transport intracellular nutrients and waste, thereby killing spoilage and pathogenic bacteria in food (34). HHP technology is widely used in numerous industries, including food preservation and sterilization and also biotechnology fields, such as pharmaceuticals.

In recent years, research on the effect of HHP on tumor cells has been increasing. HHP can induce the ICD of tumor cells. Immunogenic cell death is a type of regulatory cell death that can activate the host to generate adaptive immune responses. The ability to reshape the TME through multiple mechanisms may increase the success of immunotherapy (35). HHP-induced immunogenic cell death is driven by excessive reactive oxygen species (ROS) production, which triggers a rapid integrated stress response, protein kinase R-like endoplasmic reticulum kinase-mediated eukaryotic translation initiation factor 2 subunit-α (eIF2α) phosphorylation and the sequential activation of caspases-2, -8 and -3 (36). Fucikova *et al* (37) reported that HHP rapidly induced the surface expression of heat shock protein (HSP)70, HSP90 and calreticulin, while also promoting the release of high-mobility group box 1 and ATP. In addition, HHP treatment activated key features of the endoplasmic reticulum stress-mediated apoptotic pathway, including ROS production, eIF2α phosphorylation and caspase-8 activation. HHP has also been reported as a production technology for tumor vaccines. HHP-treated cells can be cryopreserved and retain their immunogenicity. In addition, clinical trials have reported that HHP-treated tumor vaccines induce specific immune responses to tumor cells (Fig. 2) (38).

Although HHP has shown potential in cancer treatment, it faces several limitations. HHP is mainly used *in vitro*, while precise *in vivo* methods are yet to be developed. HHP remains experimental, lacking established treatment guidelines. Further research is needed to optimize pressure control, improve application techniques and explore combination therapies to enhance safety and effectiveness.

NP. The cell membrane is a semi-permeable lipid bilayer, and the cytoskeleton and sodium and potassium pump of tumor cells are abnormal, which may lead to a decrease in the osmotic pressure regulation ability of tumor cells. Atmospheric pressure is one of the environmental factors necessary for the survival of life. The different types of tissues and cells in the body have different levels of adaptability to the living environment. Compared with normal cells, the cytoskeleton and sodium and potassium pump of malignant tumor cells are abnormal. Malignant tumor cells have a decreased ability to control their intracellular osmotic pressure compared with normal cells and are less tolerant of hypotonic stress. As atmospheric pressure and intracellular osmotic pressure exert opposite effects, the osmotic pressure regulation function of tumor cells is impaired. If the cells are in an environment with low atmospheric pressure, tumor cells rupture and die before normal cells (39). It has been reported that NP inhibits the proliferation and metastasis of pancreatic cancer cells (40). Furthermore, applying NP after injecting synthetic severe acute respiratory syndrome coronavirus 2 DNA vaccine in rats improved the immune effect of the vaccine (Fig. 2) (41). Although there is currently a scarcity of research on the effects of NP on tumor cells, the hypothesis that NP kill tumor cells without affecting normal cells appears feasible. This may potentially be a new research direction for tumor treatment.

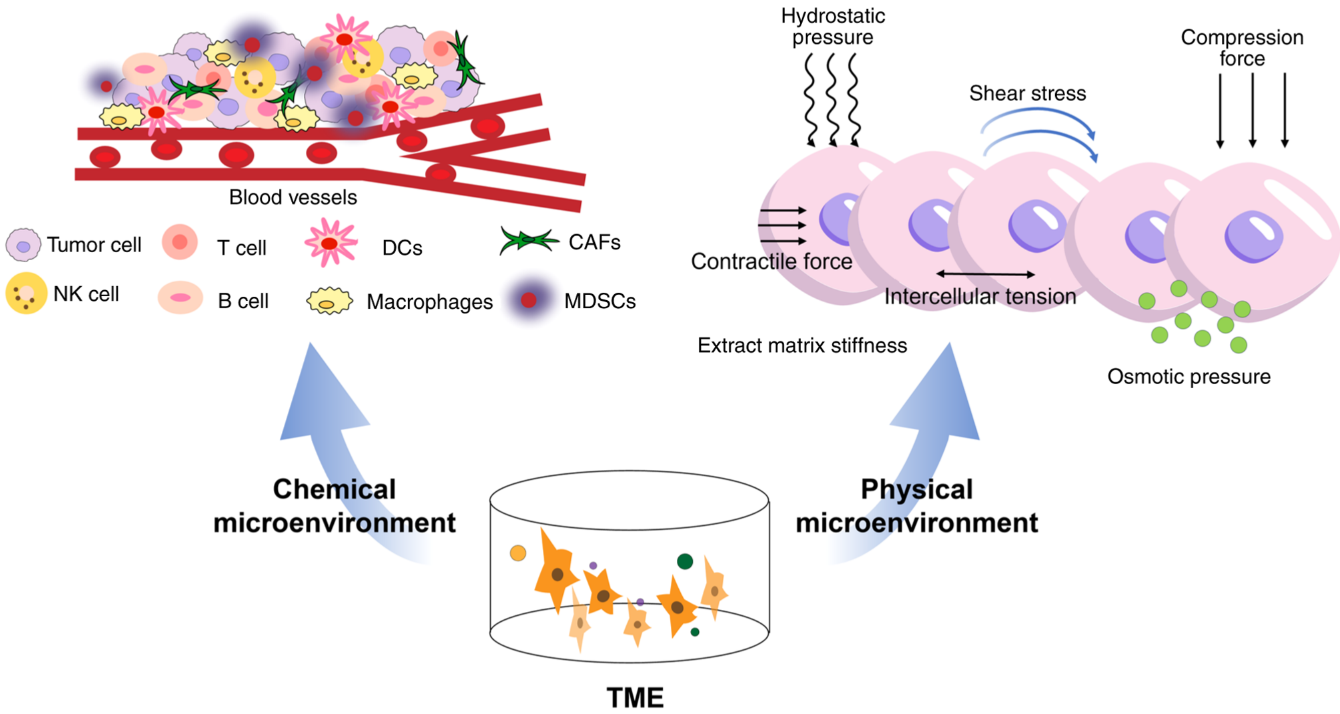

Figure 1. Composition of the TME. The TME is composed of the chemical microenvironment and the physical microenvironment. The chemical microenvironment is populated by numerous diverse cell types, including blood vessels, and immune cells, e.g., T and B cells, DCs, NK cells, MDSCs, CAFs and macrophages. The physical microenvironment includes osmotic pressure, intercellular tension, contractile force, shear stress, hydrostatic pressure, compression force and extract matrix stiffness. TME, tumor microenvironment; DCs, dendritic cells; NK, natural killer; MDSC, myeloid-derived suppressor cells; CAF, cancer-associated fibroblasts.

3. Temperature

Environmental temperature is a critical factor that influences the viability of organisms. When the environmental temperature of tumor cells reaches ~50˚C, cells experience thermal damage. When the temperature reaches 55˚C, collagen denatures, whereas when the temperature is >60˚C, cellular structures such as mitochondria change and tumor cells begin to undergo necrosis. On the contrary, when the temperature drops from -4 to -21˚C, ice crystals form outside the tumor cells and the cells begin to dehydrate. When the temperature drops to -40˚C, homogeneous ice crystals form inside the cells, which is critical for cell death. Therefore, temperature changes have an impact on the viability of tumor cells. According to the different modes of temperature action, temperature therapy is divided into hyperthermia and cryotherapy. Hyperthermia changes tumor cell membrane permeability, protein denaturation and DNA synthesis, thereby inducing cell apoptosis or necrosis. Cryotherapy results in mechanical damage to the cell membrane, thereby inducing tumor cell necrosis and apoptosis. The subsequent review sections will introduce the mechanism of action, research progress and clinical application of thermotherapy and cryotherapy to provide a theoretical and experimental basis for further exploring the potential of temperature therapy in tumor treatment.

Hyperthermia. Hyperthermia, a treatment that increases the temperature to 39-45˚C to induce cell death through apoptosis or necrosis (42), is a low-toxic tumor treatment, which is currently used clinically. According to different heating techniques and heating locations, hyperthermia techniques are divided into whole-body hyperthermia (43), local hyperthermia and local-regional hyperthermia (44). Whole-body hyperthermia is a widely explored approach in oncology, where the body temperature is elevated to 38.5-41.5˚C and maintained for a certain period. This is typically achieved using non-invasive surface heating methods, such as infrared electromagnetic waves, which penetrate the subcutaneous layer and directly heat the blood in the capillaries, thereby raising the overall body temperature. Various techniques have been developed for local hyperthermia to target tumor tissues more precisely while minimizing harm to normal tissues. These include infrared water window heating, intracavitary hyperthermia and high-intensity focused ultrasound (45).

Hyperthermia indirectly kills tumor cells. Heating causes reactive expansion of blood vessels in normal tissue around the tumor, which causes further reduction of blood flow in the tumor tissue, leading to hypoxia in the tumor tissue. This induces a state of hypoxia, hyponutrition and low blood flow for an extended period of time, causing the accumulation of lactic acid and inducing TME changes. The pH drops, inducing tumor acidosis (46). Hyperthermia can also upregulate the expression levels of HSP70, thereby increasing the immune antigenicity of tumor cells, inhibiting their proliferation and migration and inducing tumor cell death (47). In mouse models of nasopharyngeal carcinoma, hyperthermia can upregulate the expression levels of HSPA5, downregulate CD55 expression levels through HSPA5/NF-κB signal transduction and activation of the complement cascade and inhibit tumor development (Fig. 3) (48).

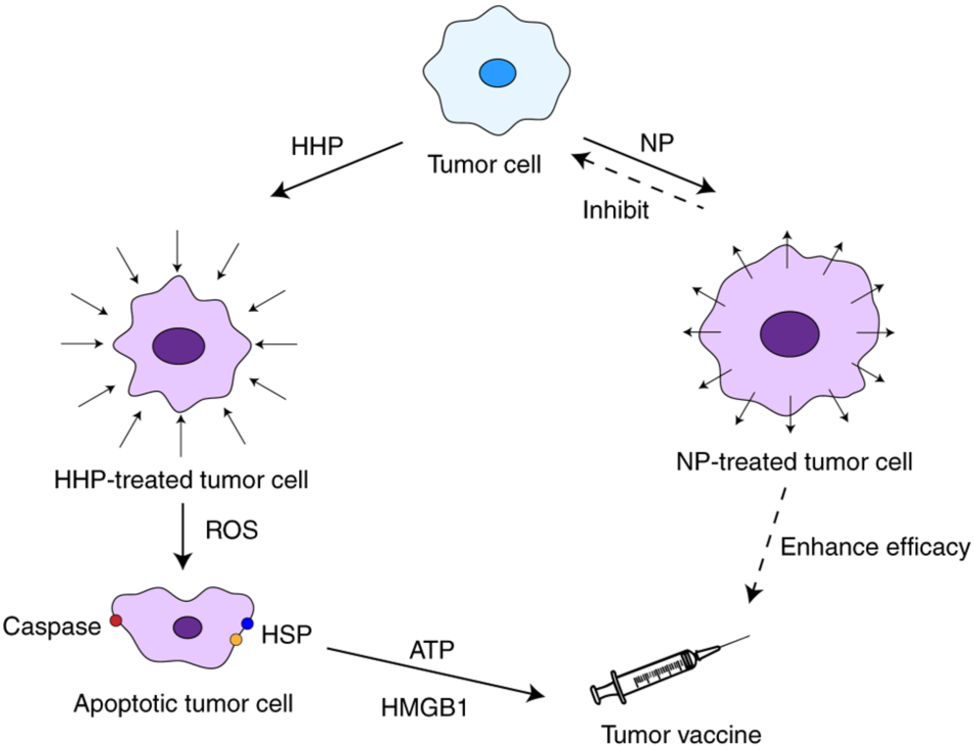

Figure 2. Characterization of pressure treatment and its effects on tumor cells. HHP reduces protein synthesis and structure and denatures proteins. HHP treatment effectively induces tumor cell killing and is considered a novel method for the preparation of autologous tumor cell vaccine. NP treatment also enhances vaccine efficacy. HHP, high-pressure therapy; NP, negative pressure therapy; ROS, reactive oxygen species; HSP, heat shock protein; HMGB1, high-mobility group box 1.

Hyperthermia can also directly kill tumor cells, as it can inhibit the synthesis of RNA, DNA and protein, preventing the proliferation of tumor cells (46). When the temperature of the body is maintained at >40˚C for a certain period of time, the cytoskeleton of tumor cells is destroyed, causing their protein to denature and cell complex enzymes to be affected, thus inhibiting the DNA synthesis process until the cells die. It has also been shown that hyperthermia can induce apoptosis of tumor cells by activating the caspase family of proteins (Fig. 3) (49).

Hyperthermia increases the efficacy of chemotherapy and radiotherapy. Hyperthermia and radiotherapy have different sites of action in the cell proliferation cycle. Hyperthermia mainly affects S-phase cells (46), whereas radiotherapy mainly affects G_1 and G_2/M phase cells (50). The combination of the two has synergistic effects on the cell cycle. A study on breast cancer cells showed that radiofrequency heating at 13.56 MHz and 43˚C for 20 min significantly reduced the S-phase cell population, while at the same time significantly increasing the G_2/M-phase cell population, enhancing the efficacy of radiotherapy (51). Of all types of DNA damage, DNA double-strand breaks are considered the most harmful (52). Heating can cause double-stranded DNA breaks or reduce DNA damage repair (53). The ionization effect of radiation in organisms exerts its killing effect on tumor cells by directly or indirectly causing cell DNA strand breaks. DNA is the main target of ionizing radiation and ionizing radiation has a cytotoxic effect, causing single- and double-strand DNA breaks (54). Although radiation causes a certain degree of direct killing effect on tumor vascular endothelial cells, it also induces the expression of vascular endothelial growth factor (VEGF), making tumor vessels more resistant to radiation. Hyperthermia can inhibit the expression of tumor-derived VEGF and its products, thereby hindering the proliferation of tumor vascular endothelium and reshaping of extracellular matrix, inhibiting tumor growth and metastasis. Liang *et al* (55) reported that hyperthermia can inhibit VEGF gene expression and protein synthesis levels, indicating that heating can inhibit the proliferation of endothelial cells and the formation of tumor neovascularization, thereby enhancing the radiation effect on tumors. Heating changes the permeability of cell membranes, making it easier for drugs to enter tumor cells and improving the penetration and absorption of chemotherapeutic drugs. Therefore, hyperthermia and chemotherapeutic drugs serve a synergistic role in increasing the cytotoxicity of chemotherapeutic drugs and exerting antitumor effects. In addition, hypoxia in tumor cells is an important factor leading to drug resistance. Therefore, adding hyperthermia treatment alongside chemotherapy can also eliminate chemotherapy resistance and improve the efficacy of drugs (Fig. 3) (56).

As a supplement to existing tumor treatment plans, thermotherapy has a promising prospect in the clinical treatment of advanced relapsed tumors. A meta-analysis analyzed the efficacy of thermal radiation therapy and showed that the overall complete response rate in the thermal radiation therapy group was 54.9%, which was significantly higher compared with that of the single radiation therapy group, at 39.8% (57). Although hyperthermia is a promising cancer treatment, it has several limitations and side effects, such as maintaining an optimal therapeutic temperature while avoiding damage

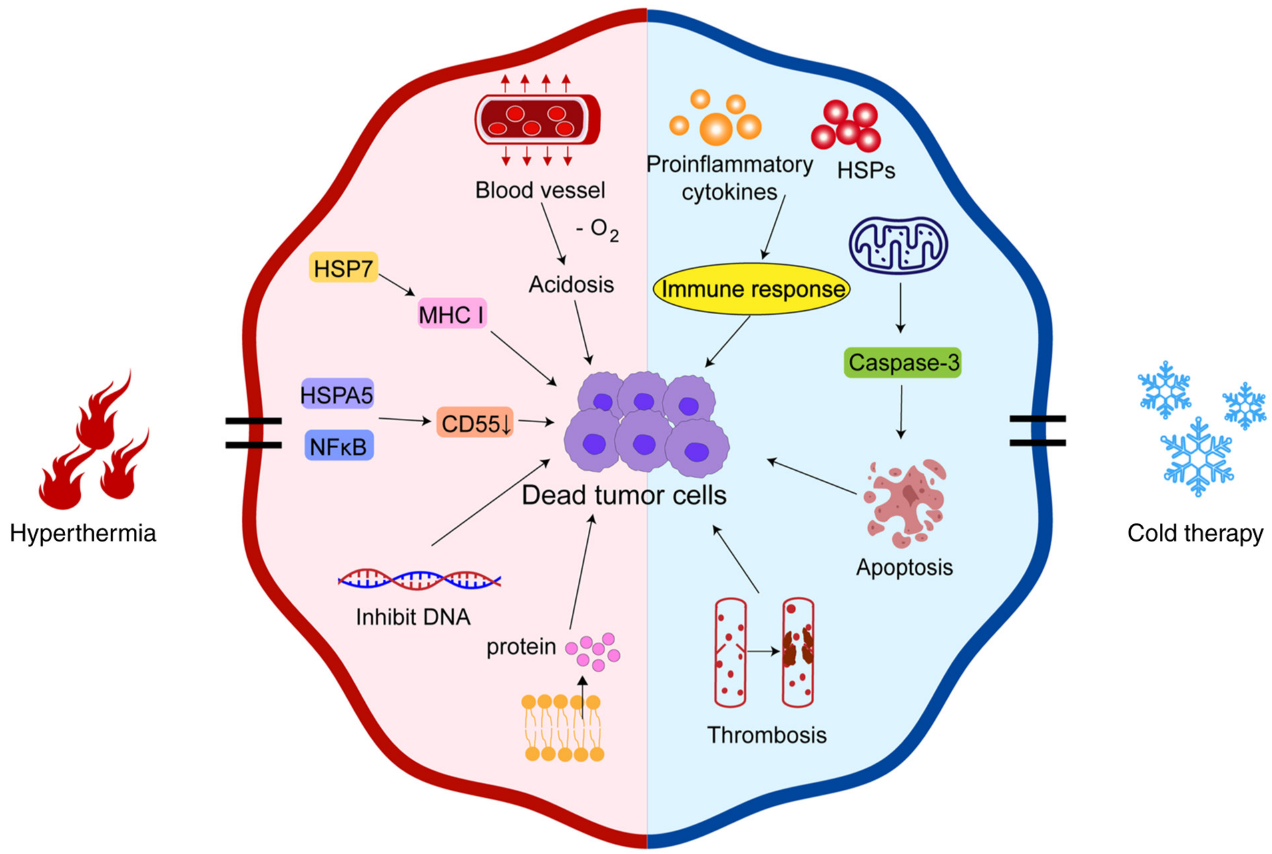

Figure 3. Schematic representation of the temperature of tumors. Hyperthermia causes vasodilation in the tissues surrounding the tumor, inducing acidosis, upregulating HSP70 and HSPA5, downregulating CD55 and inhibiting DNA synthesis, inducing tumor death. Cold therapy induces tumor cell death by influencing the immune response, inducing apoptosis and causing thrombosis. HSP, heat shock protein; MHC, major histocompatibility complex.

to surrounding tissues, burns, pain and thermal damage to healthy tissues. Further studies are required to determine the future of thermal therapy, such as expanding the application of thermal therapy in cancer treatment, combining thermal therapy with other treatment methods to obtain more accurate data and provide a basis for clinical treatment.

Cold therapy. Cryoablation technology is increasingly being utilized in the minimally invasive treatment of tumors. At present, cryoablation technology mainly includes liquid or gas as a medium to quickly drop the local temperature of the tumor to <-140˚C to generate ice crystals. This causes the cell membrane to rupture and occlude the microvessels in the ablation area, resulting in ischemia and necrosis of tumor cells. Cryoablation induces tumor cell death through multiple mechanisms. Cryoablation can induce cell membrane damage to tumor cells, activate the immune response, induce apoptosis and cause vascular embolisms.

After cryoablation forms ice crystals, the cell membrane undergoes mechanical damage and activates a series of antitumor immune reactions, causing tumor necrosis (58). Cells that are not directly killed by cryoablation may induce apoptosis through a pathway mediated by mitochondria that activates the caspases family (59). Cryoablation can also cause vascular embolism, leading to diminished blood flow to the tumor and amplifying its cytotoxic effect on the tumor. When the temperature drops, the tissue's extracellular fluid freezes and the development of extracellular ice elevates the osmotic pressure external to the cell, causing the fluid to transfer from the inside to the outside of the cell. In this hypertonic environment, alterations in the intracellular pH and cellular constituents may result in cellular injury (60). Cryoablation can also cause changes in the immune function of tumors. Cells that die due to osmotic shock or mechanical damage from ice crystals release their intracellular contents into the extracellular space. Numerous types of content are immunostimulatory, such as pro-inflammatory cytokines, HSPs and other related factors. Their receptors can activate the immune response (61). Studies have shown that after cryoablation, tumor antigens are released and the activation of lysosome-related pathways leads to the overexpression of the synaptosome-associated protein 23 and syntaxin binding protein 2, thereby promoting the activation of immune effector cells and suppressing the release of immunosuppressive factors, ultimately leading to enhanced antitumor immunity (62). In addition, Seki *et al* (63) reported that the glucose catabolic ability of brown adipose tissue is enhanced under low-temperature environments, resulting in decreased blood sugar and insulin tolerance. This reduces the metabolism of the body, thereby decreasing the catabolic ability of glucose in the tumor, inhibiting tumor growth and providing a potential new treatment method for cancer therapy (Fig. 3).

There are numerous reports on the application of cryoablation in numerous organs, but the effect of cryoablation treatment using cryoablation is not identical and is closely associated with the heterogeneity of the tumor. Guo *et al* (64) summarized the clinical application status of cryoablation, indicating that cryoablation technology has advantages such as minimal invasiveness and fewer complications. The cooling rate, target temperature, time at target temperature, thaw rate and number of cycles are the main parameters that directly affect the therapeutic effect of cryoablation technology. In the future, auxiliary treatment of cryoablation may rely on the optimization of these parameters to maximize the surgical efficacy and minimize surgical complications, reducing the tumor burden.

4. Phototherapy

Phototherapy is a method of exposing a patient to light to treat disease. Phototherapy has been reported to be a safe tumor treatment in a number of previous studies, mainly focusing on photothermal therapy (PTT) and photodynamic therapy (PDT) (65). PTT irradiates the photothermal agent (PTA) with light at a specific wavelength, which heats the PTA and kills tumor cells, whereas PDT produces a large number of ROS under the specific wavelength to kill tumor cells (66). Photosensitizers are key to PDT and PTT can improve treatment efficiency and efficacy without the requirement of any external photothermal contrast agents (66). During clinical treatment, PTA and photosensitizers are typically administered through intravenous or local applications. Through active or passive targeted delivery, they accumulate in tumor tissue and light of a specific wavelength is used to irradiate the tumor tissue locally. The following sections in this review will introduce the mechanism of action, research progress and clinical application of PTT and PDT, providing a theoretical basis and practical reference for the further development of phototherapy in tumor treatment.

PTT. PTT uses photothermal conversion nanomaterials targeted to tumor sites to absorb and convert light energy into heat under near-infrared irradiation, thereby inducing tumor cell death (67). It has become a highly efficient and minimally invasive method for the treatment of primary tumors (68) and has few side effects, a high specificity and can be repeated. In PTT, PTA enhances the heating of local cells and tissues. Through the local use of photosensitizers and minimally invasive near-infrared radiation, PTT-induced hyperthermia can be controlled to minimize damage to non-targeted tissues.

As aforementioned, hyperthermia can induce tumor cells to release antigens, pro-inflammatory cytokines and immunogenic intracellular substrates, promoting immune activation and causing apoptosis. PTT treatment causes effects akin to those of hyperthermia. Ali *et al* (69) irradiated MCF-7 human breast cancer cells with PTT and showed that subsequent to 2 min of laser irradiation, the cells primarily underwent apoptosis. Further research on biomarkers of the apoptosis pathway showed that the mitochondrial pathway mediates PTT-induced apoptosis through activation of Bid (70). HSPs are a category of proteins synthesized by cells in response to stress sources and are involved in the mechanism of PTT-induced cell death. Wang *et al* (71) synthesized indocyanine green-loaded vanadium oxide nanoparticles (VO_2NPs) for pH-activated near-infrared luminescent imaging-guided enhanced photothermal tumor ablation. In the acidic TME, VO_2NPs decompose and release VO^{2+}, which inhibits the function of HSP60. PTT can also induce the activation of immune function. Deng *et al* (72) loaded SNX-2112, an HSP90 inhibitor, on a graphene oxide carrier for near-infrared (NIR) irradiation. The results showed that NIR can induce downregulation of the expression levels of HSP90 and programmed cell death ligand 1 in tumor cells, whilst upregulating the expression of CD69, an activation marker of T cells. In addition, the increase in tumor blood flow caused by PTT also leads to an increase in microvascular permeability and improves drug accumulation in tumors (Fig. 4) (73).

To solve the limitations of PTT monotherapy, a series of PTT-based combination therapies have been studied. Nam *et al* (74) reported that PTT in combination with chemotherapy can trigger effective antitumor immunity against disseminated tumors. A polydopamine-coated spiked gold nanoparticle, SGNP@PDA, combined with the chemotherapy drug doxorubicin, has been developed for the chemotherapy combined with PTT. This combination therapy enhances the antitumor effect of the drug and eliminates local and untreated distant tumors, achieving survival rates >85% in a bilateral mouse tumor model of CT26 colon cancer.

In clinical trials, PTT combined with immunotherapy can produce synergistic effects, reduce primary tumors, control untreated metastasis and prolong patient survival. It can be used to treat various types of tumor, such as lung, breast, esophageal, colon and bladder cancers (75). PTT shows promise for antitumor therapy but faces certain difficulties in the clinical application of the treatment. For instance, in clinical practice, it is difficult to master the light conditions required for the conversion of photosensitizers. However, with the continuous development of nanotechnology, the clinical progress of PTT for tumor treatments will likely improve over time.

PDT. PDT is a relatively new minimally invasive treatment method that relies on the selective accumulation of photosensitizers in cancer cells to generate cytotoxic ROS when excited by light of certain wavelengths to ultimately kill cancer cells (76). PDT is based on three main components: Light, photosensitizer and oxygen. There are three mechanisms of action by which PDT destroys tumor cells: i) ROS produced by the photochemical reaction of PDT can directly kill cells by inducing apoptosis and necrosis; ii) PDT damages tumor-related blood vessels, resulting in interruption of the oxygen and nutrient supply, which leads to indirect cell death caused by hypoxia; and iii) PDT can induce an inflammatory response and activate the immune response against tumor cells (77).

Light activates the photosensitizer from the ground state to the excited state and energy transfers to molecular oxygen to form ROS. In addition to causing oxidative damage to macromolecules in tumor cells (78), ROS can also directly kill tumor cells by inducing necrosis or apoptosis. During PDT, most photosensitizers destroy mitochondrial function, cause cells to release cytochrome *c* and activate the caspase pathway to induce apoptosis of tumor cells. Liu *et al* (79) used photosensitizer aloe-emodin (AE)-mediated PDT to inhibit human oral squamous cell carcinoma both *in vitro* and *in vivo*. AE-PDT can kill tumor cells and inhibit their migration. In the PDT-treated group, the protein expression levels of Bcl-2

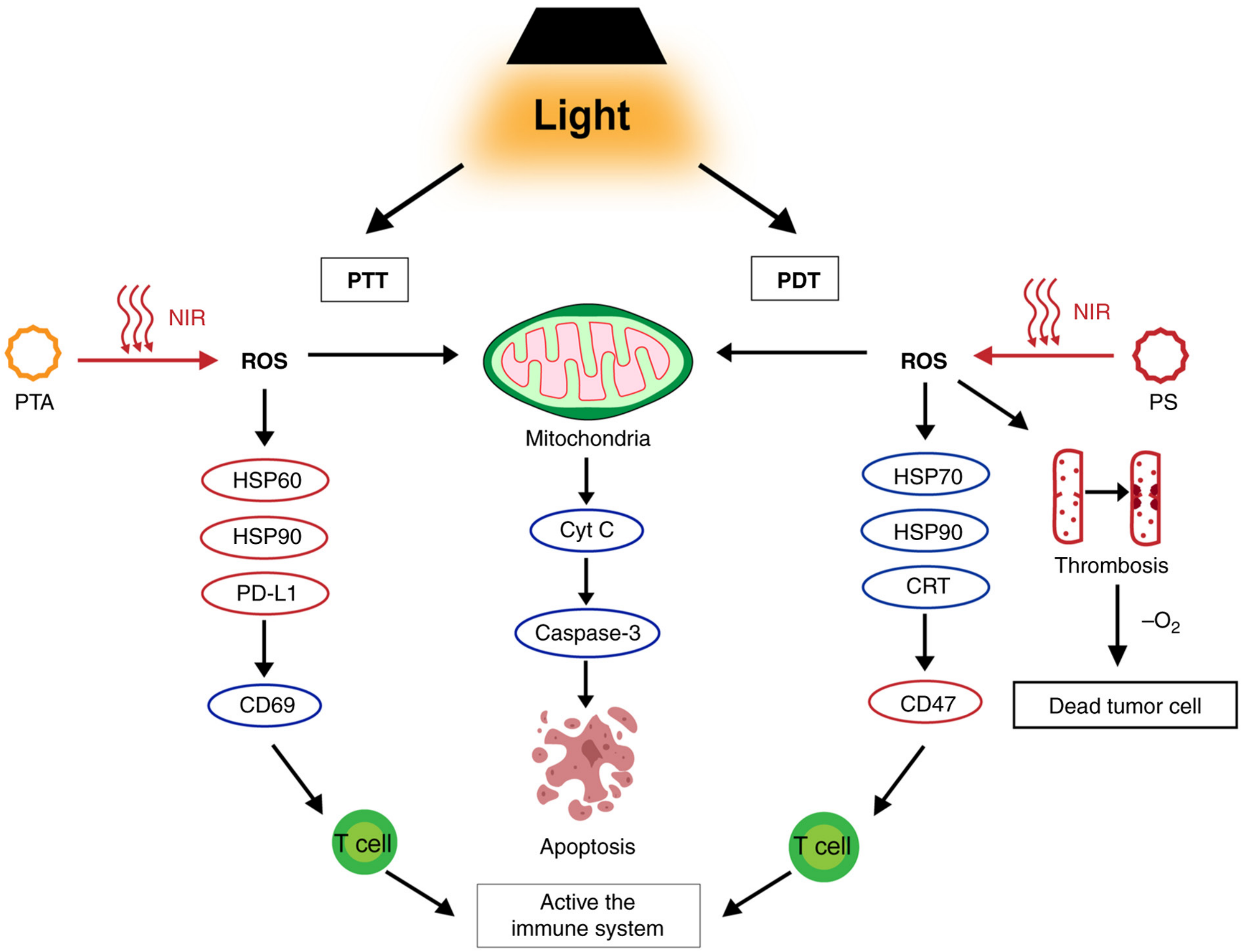

Figure 4. Mechanism of phototherapy. Phototherapy is categorized into PTT and PDT. PTT involves NIR irradiation of the PTA, increases the temperature, activates caspase-3 via the mitochondrial pathway, inhibits HSP60 and induces cell death. It inhibits HSP90 and PD-L1, upregulates CD69 and activates immune function. PDT involves NIR irradiation of the PS and produces ROS, which kills cells by inducing apoptosis and necrosis. It can form a thrombus and eventually lead to cell death. It also upregulates HSP70, HSP90 and CRT, activating the immune system. PTT, photothermal therapy; PDT, photodynamic therapy; NIR, near-infrared; PTA, photothermal agent; HSP, heat shock protein; PS, photosensitizer; ROS, reactive oxygen species; PD-L1, programmed cell death ligand 1; Cyt C, cytochrome C; CRT, calreticulin.

and Bcl-2/Bax were significantly decreased, while the protein expression levels of Bax and Caspase-3 were significantly increased. De Miguel *et al* (80) studied the effect of PDT on skull and spinal osteosarcoma in Balb/c nude mice and reported that the volume of bone matrix increased after PDT treatment and the size of the tumor decreased, which may be related to increased necrosis (Fig. 4).

During PDT, when activated by light, the endothelial cells of the tumor vascular system produce ROS, destroying the tumor vascular endothelial cells and causing thrombosis. This results in a series of corresponding physiological reactions, such as the release of vasoactive molecules and increased vascular permeability (81), leading to the interruption of the supply of oxygen and nutrients to the tumor and death of tumor cells. Dolmans *et al* (82) used the photosensitizer MV640, which targets blood vessels, to study the mechanism of PDT damage of tumor blood vessels. The tumor tissue showed dose-dependent effects of this treatment, such as blood stasis, ischemia, internal tumor hemorrhage, disappearance of blood vessels and thrombosis, and inhibited tumor growth due to ischemia and hypoxia. Other studies have shown that PDT can reduce the expression levels of NF-κB through a ROS-mediated mechanism and activation of NF-κB serves an important role in the tumor mechanism induced by blood vessel photosensitivity (Fig. 4) (83,84).

In addition, PDT can also disrupt immune homeostasis within tumors, activate corresponding immune and inflammatory reactions and produce anti-tumor effects. Zheng *et al* (85) performed a study of PDT in the treatment of Lewis lung cancer in mice and showed that a large number of damage-related proteins were released after the tumor cells were damaged, which in turn mediated the body's antitumor immune response (Fig. 4).

PDT has been reported to achieve clinical efficacy in the treatment of skin, esophageal and bladder cancers. A preliminary study demonstrated the effectiveness and safety of PDT in patients with bladder cancer who had complete transurethral resection and were confirmed without serious adverse reactions (86). PDT is an effective and safe alternative to traditional treatments with a low incidence rate of tumors, but its widespread use is currently limited due to the high cost of photosensitizers and light source equipment required by PDT. Photosensitizers may also cause skin light allergies and the tissue penetration of light is limited; therefore, PDT is restricted in its application for certain types of deep tumor such as glioma. With the development of new photosensitizers, light source technologies and combined treatment strategies, PDT may have broad future application prospects (87).

5. Sonodynamic therapy (SDT)

As a new non-invasive therapy derived from PDT, SDT has been previously researched and explored. The principle of SDT is similar to that of PDT. SDT uses low-intensity ultrasound to stimulate disease sites, activate sonosensitizers and generate ROS, inducing tumor cell death. Different types of sonosensitizers, including organic molecules and inorganic nanomaterials, such as piezoelectric materials, semiconductors and metallic materials, have been explored over the past few years. Due to the rapid development of nanotechnology, a variety of nanomaterials have been prepared into sonosensitizers or nanocarriers for sonosensitizers, markedly improving the targeting, stability and biological safety of sonosensitizers. Chen *et al* (88) used stanene-based nanosheets as nano-sound sensitizers to enhance the antitumor efficacy of SDT. The antitumor mechanism of SDT occurs under low-intensity ultrasound irradiation as the caspase pathway is activated and apoptosis of tumor cells is induced. Li *et al* (89) reported that sinoporphyrin sodium-mediated SDT significantly increased intracellular ROS. The elevated production of ROS increases the expression levels of p53 and Bax while suppressing Bcl-2 expression, resulting in the activation of caspase-3 and ultimately triggering cellular apoptosis. Yang *et al* (90) reported that SDT mediates and induces apoptosis, which is related to the formation of cell membrane pores caused by the destruction and cavitation effect of microbubbles (Fig. 5).

Autophagy is the process of degradation of proteins or organelles within cells and is an important defensive and protective mechanism of cells (91). Autophagy starts from the endoplasmic reticulum and regulates the formation of autophagy bodies under the collaborative action of the UNC51-like kinase-1 kinase, PI3K and autophagy-related protein 9 complexes (92,93). It has been shown that SDT can induce autophagy through the MAPK/p38-PTEN-induced putative kinase 1-parkin RBR E3 ubiquitin protein ligase mitochondrial autophagy and PI3K/Akt/mTOR pathways (94). Ferroptosis is a non-apoptotic regulated cell death caused by iron accumulation and subsequent lipid peroxidation (95). Sun *et al* (96) prepared a metal-organic framework biomimetic nanosystem, mFeP@si, as a sonosensitizer, mediating the rupture of lysosomal membranes to achieve lysosomal escape, accelerating ROS production and glutathione depletion and further triggering iron death (Fig. 5).

As an emerging technology, SDT is still in the exploration stage. Research on SDT in brain tumors, such as glioblastoma, is underway and preliminary results show that SDT can penetrate the blood-brain barrier and has potential therapeutic value (97). Despite facing challenges, such as sound sensitizer development and ultrasound parameter optimization, SDT may potentially become an important supplementary therapy for the treatment of tumors as research progresses. In the future, the scale of clinical trials needs to be further expanded to verify their safety and efficacy.

6. Other new therapies

With continuous tumor treatment research, other types of new physical therapies have also attracted attention. These include magnetic therapy, acupuncture and local interventional therapy, which impact the growth, invasion and metastasis of tumor cells through different biophysical mechanisms. The following sections will introduce the mechanisms of action of these novel therapies and their potential applications in tumor therapy.

Magnetic therapy. Magnetic therapy involves an external physical stimulus and produces complex biological effects. It has been shown that appropriate magnetic field stimulation can prevent inflammation and oxidative stress and alleviate or repair neurological damage, and magnetic fields may have protective effects in various diseases. Magnetic therapy for cancer includes pulsed electric field (PEF) and pulsed electromagnetic field (PEMF).

The PEF is generated by applying a voltage to two electrodes. Under the action of PEF, the permeability of the cell membrane increases, causing mitochondrial vacuoles to produce and release cytochrome *c*. When acting on the nucleus, DNA double strand breakage may occur. PEF can block the transfer of cells from G_0/G_1 phase to $S+G_2/M$ phase. Kulbacka *et al* (98) reported that nanosecond PEF reverses drug resistance in gastric cancer cells by inducing oxidative stress and apoptosis. PEF can also regulate immune function and induce antitumor effects. Pastori *et al* (99) showed that PEF has an immunomodulatory effect on a breast cancer model of mice, inhibiting tumor growth and improving the survival rate of mice (Fig. 6).

PEMF is used to treat various diseases, including osteoarthritis (100) and Parkinson's disease (101). Both *in vitro* and *in vivo* research on PEMF-related tumors is becoming more widespread. PEMF can inhibit cell proliferation, block tumor angiogenesis, alter the cell cycle, directly kill or induce tumor cell apoptosis and exert antitumor effects. Filipovic *et al* (102) studied the effect of a 50-Hz magnetic field on different cancer cell systems, indicating that PEMF therapy has an antiproliferative effect, which inhibits cell division by destroying the mitotic spindle structure, leading to chromosome separation errors and inducing apoptosis. Guo *et al* (103) reported that the cell cycle of cancer cells is affected under low-frequency magnetic fields. PEMF also increases doxorubicin-induced DNA damage by inhibiting DNA topoisomerase II alpha. In another study, 8 Hz PEMF was used to irradiate MCF-7 and MDA-MB-231 breast cancer epithelial cells and FF95 normal fibroblasts. It was found that the proliferation rate and activity of breast cancer cells were reduced, whilst the death and aging of breast cancer cells were induced (Fig. 6) (104).

Currently, the clinical application of PEMF is limited and Barbault *et al* (105) published the first report using PEMF therapy and magnetic fields of specific frequencies to show the therapeutic effect of PEMF in local tumor treatment. Clinical research has also revealed that PEMF relieves pain associated

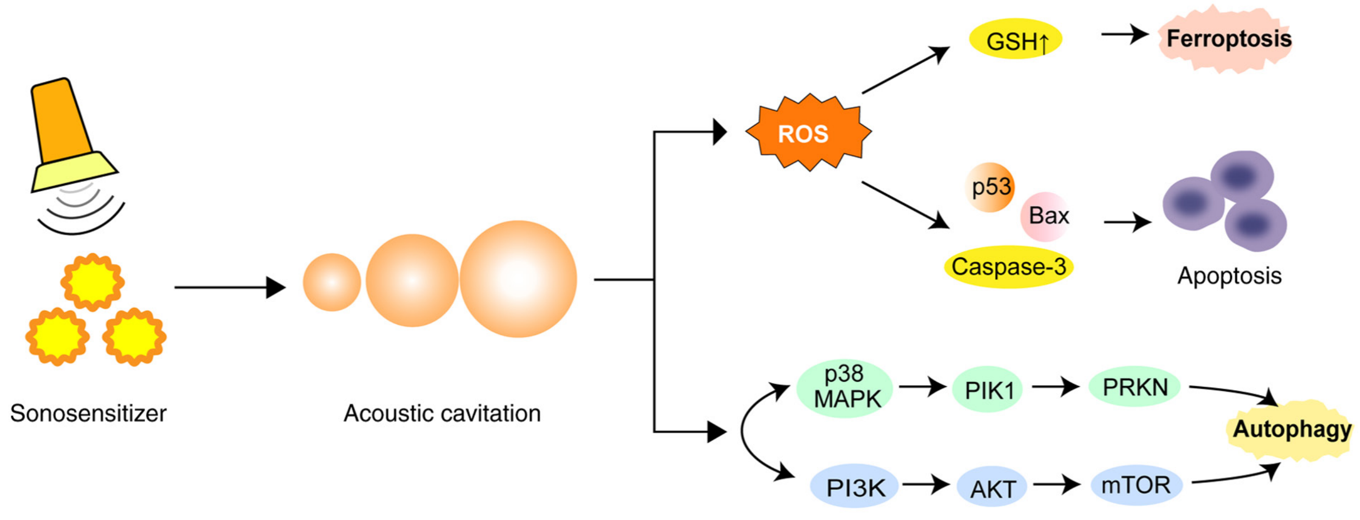

Figure 5. Mechanism of sonosensitizers. SDT can mediate the antitumor response, activates sonosensitizers and generates ROS through apoptosis, ferroptosis and autophagy, thereby inducing tumor cell death. SDT, sonodynamic therapy; ROS, reactive oxygen species; ROS, reactive oxygen species; GSH, glutathione; p53, tumor protein p53; Bax, bcl-2-associated x protein; p38, tumor protein p38; MAPK, mitogen-activated protein kinase; PIK1, PTEN-induced kinase 1; PRKN, parkin RBR E3 ubiquitin protein ligase; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin.

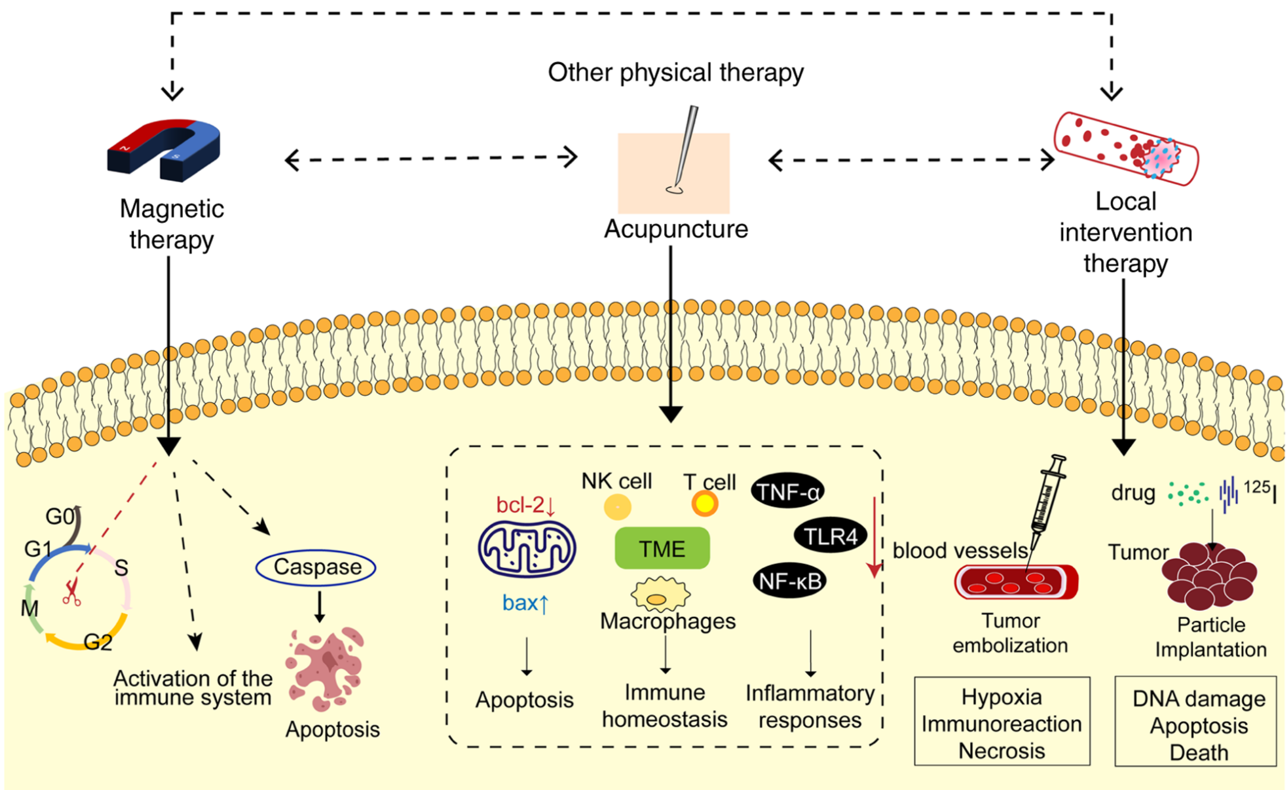

Figure 6. Mechanisms of the antitumor effects of magnetic therapy, acupuncture and local intervention therapy. These treatments all serve key roles in antitumor effects through apoptosis, influencing the cell cycle and activating the immune system. NK, natural killer; TME, tumor microenvironment; TLR, Toll-like receptor.

with cancer (106). Although the biological effects of PEMF have been verified in certain studies, its specific mechanism still needs to be explored in depth. PEMF therapy provides a safe and well-tolerated approach for tumor treatment.

Acupuncture. Acupuncture involves the stimulation of certain acupoints, activating peripheral nerves, sending sensory information from the spinal cord to the brain, engaging peripheral autonomic nerve pathways and modulating the body's physiological state (107). According to the concepts of Traditional Chinese Medicine, acupuncture has the functions of strengthening the body, dredging the meridians, promoting the movement of qi and blood and harmonizing the visceral organs. Clinical studies on the treatment of tumor complications with acupuncture have shown that acupuncture can effectively improve the symptoms of tumor complications and delay the growth of tumors to a certain extent, acting as a safe and efficient physical therapy method (108). Acupuncture primarily exerts an antitumor effect by enhancing and optimizing the tumor immune microenvironment, improving the local angiogenesis of the tumor and promoting tumor cell apoptosis. In the immune microenvironment, NK cells, $CD8^+$ T cells, $CD4^+$ T cells, macrophages and related cytokines are associated with the treatment of tumors by acupuncture and moxibustion (109). A study using Lewis lung cancer model mice showed that acupuncture and moxibustion can promote the production of NK cells by regulating adrenergic signals, restoring the immune homeostasis of the body and improving its antitumor capabilities (110). Electroacupuncture at 'Zusanli' can alleviate renal injury in mice with colorectal cancer after 5-fluorouracil chemotherapy, and its mechanism of action may be related to regulating renal oxidative stress, reducing the inflammatory response and inhibiting apoptosis (111). Acupuncture may also reduce the overexpression of NF-κB and the excessive release of inflammatory factors by inhibiting the overexpression of TNF-α and Toll-like receptor 4, thereby reducing the occurrence of liver inflammation in cis-diaminodichloroplatinum (DDP) mice, reducing the side effects of DDP on the liver and serving an effective role in liver protection (112). Acupuncture can significantly reduce the protein expression levels of Bcl-2 in tumor cells of tumor-bearing mice, increase the protein expression levels of Bax, reduce the ratio of Bcl-2/Bax and promote tumor cell apoptosis (113). Previous clinical studies have reported that acupuncture and moxibustion have an effect on the symptoms associated with tumors, including gastrointestinal adverse reactions (114), cancerous pain (115), insomnia (116) and anxiety (117). Therefore, the use of acupuncture and moxibustion to treat tumors may provide new ideas for clinical practice, providing a basis for further study (Fig. 6).

Local intervention therapy. As a type of tumor physical therapy, local interventional therapy relies on imaging guidance to accurately deliver the therapeutic device to the tumor site, achieving direct effects on the lesions, including tumor embolization and granule implantation.

Tumor embolization is an imaging-guided local interventional treatment method. This involves injecting embolization materials or drugs directly into the tumor blood supply artery, blocking the tumor blood supply and inducing hypoxic necrosis. The tumor blood supply artery is selectively blocked by embolizers and forms a thrombus to induce tumor hypoxia and nutritional deficiency (118). Cancer cells in a stressed state can affect cell migration, angiogenesis and metastasis by activating the antitumor immune response. It has been reported that in a rat model of liver cancer, hepatocellular carcinoma cells develop hypoxia stress due to embolisms (119). Avritscher *et al* (120) reported that after embolization treatment, tumor-infiltrating lymphocytes and IL-17 expression levels in type 17 T-helper cells increased, activating the antitumor immune response and reducing cell migration. Tumor embolization has important clinical value in a variety of solid tumors. Maclean *et al* (121) used a novel absorbable gel microsphere to embolize 23 patients undergoing uterine fibroid embolization. These results showed that tumor necrosis occurred in 83% of the patients (Fig. 6).

Particle implantation treatment achieves precise local treatment by implanting radioisotope or antitumor drug carrier microparticles directly into the tumor. Granule implantation treatment depends on the role of radioactive or drug particles in the tumor. The implanted particles act directly on tumor cells, causing DNA damage and further inducing apoptosis.

Zhang *et al* (122) showed that implanting ^{125}I radioactive particles in a mouse model of liver cancer upregulated the expression levels of proinflammatory cytokines in cancer cells and enhanced cytokine-induced killer cell-mediated apoptosis by activating caspase-3. In a retrospective study, 27 patients with bone metastatic tumors were treated with ^{125}I particles to treat pain relief after surgery without any serious complications (Fig. 6). Local interventional treatment has few complications. Through precise positioning, it provides minimally invasive and individualized treatment plans for patients with solid tumors, but it also has limitations (123). In the future, through strategies such as the combination of drugs, immunotherapy and improving drug delivery, this treatment may improve the efficacy of tumors, reduce adverse reactions and provide more accurate and efficient individualized treatment plans for patients with refractory tumors.

7. Conclusion and perspectives

Tumors cause a multi-factor, long-term type of disease. In certain cases, it is impossible to completely kill all tumor cells, which can lead to excessive medical treatments administered to patients. Compared with other diseases, the currently existing measures such as surgery, radiotherapy, chemotherapy and biotherapy do not have high efficacy rates. Therefore, finding new types of effective treatments is of high priority. With the advancement of the social economy, science and technology, modern mechanized manufacturing provides material guarantee and infinite possibilities for physiotherapy. Instruments and equipment can be used repeatedly and their applications in healthcare are more promising compared with chemotherapy. Physiotherapies may potentially be used in palliative therapy for advanced tumors, due to their decreased side effects and the low cost of treatment (124).

Physical therapy, as an emerging cancer treatment method, has become a research hotspot. Compared with application bottlenecks associated with treatments such as chemotherapy and biotherapy, physical therapy can achieve precise localized treatment with minimal systemic toxicity and side effects. The present review summarized the antitumor mechanisms of physical therapy methods such as pressure, temperature, light, sound and magnetism, demonstrating the broad research potential and applicability of physical therapy for tumors. Although physical therapy has made significant progress in experimental research, there are relatively few clinical trials for these treatment types. First, clinical trials are limited to the current level of understanding and technology. Second, within a certain range, the degree of influence of physical factors is insufficient. Since physical therapy often relies on instruments and materials that alter the internal physical factors of tumors, further basic and clinical research is required to determine the mechanism of action of physical therapy in tumor treatment and its potential for clinical applications. Future research on the physical therapy of tumors may provide a strong scientific basis for the use of these therapeutic methods in the treatment of tumors.

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Availability of data and materials

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Authors' contributions

JX, CJ and GC were involved in the conception and design of the study, drafting and revision of the manuscript and preparation of the figures. HS, YW, CS, ShaL, TY, YS, YL and YF drafted and revised the manuscript. QZ, ShuL and TX revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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