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REVIEW

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Emerging trends in materials and devices-based electric stimulation therapy for tumors

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Abstract

Electrical stimulation (ES), as one of the physical therapy modalities for tumors, has attracted extensive attention of researchers due to its promising efficacy. With the continuous development of material science, nanotechnology, and micro/nano processing techniques, novel electroactive nanomaterials and delicately designed devices have emerged to realize innovative ES therapies, which provide more possibilities and approaches for tumor treatment. Meanwhile, exploring the molecular biological mechanisms underlying different ES modalities affecting tumor cells and their immune microenvironment is also an unresolved hotspot emerging from the current biomedical engineering research. Focusing on the above research interests, in this review, we systematically summarized the effects of different ES

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parameters on the subcellular structure of tumor cells and the tumor immune microenvironment (TIME) in conjunction with the involved signaling pathways. In addition, we also reviewed the latest progress in novel self-powered devices and electroactive nanomaterials for tumor therapy. Finally, the prospects for the development of electrostimulation tumor therapy are also discussed, bringing inspiration for the development of new physical therapy strategies in the future.

KEYWORDS
cancer therapy, electrical stimulation, electroactive materials, self-powered device

1 | INTRODUCTION

Cancer is one of the three major killers threatening human health today. Unlike normal tissues, tumors are difficult to be cure due to their complex structure and composition.[1] Although significant progress has been made in the development of cancer treatments, there is still a need for more effective and safer therapies. One promising area of research that has gained attention in recent years is electrical stimulation (ES) therapy, which includes direct ES such as irreversible electroporation (IRE), tumor treating fields (TTFields), electrochemical therapy (EchT), and indirect ES therapy based on self-powered device (nanogenerator, galvanic cell) and electrically responsive nanomaterials (photoelectric nanomaterials, pyroelectric nanomaterials, piezoelectric nanomaterials and electrocatalytic nanomaterials). Some of these therapies have been widely adopted in clinical practice. For example, electrochemotherapy (ECT) based on reversible electroporation increases the permeability of the membrane by applying a pulsed electric field,[2] which facilitates the entry of poorly permeable therapeutic agents into the cell, and ultimately kills the cancer cells. Based on electroporation, IRE[3] is currently the only non-thermal ablation technique and has become an emerging clinical treatment option. By applying high-voltage electrical pulses, irreversible micropores can be formed in the cell membrane. These micropores induce the apoptosis of cancer cells, thereby activating the immune system to eliminate the apoptotic cells. Moreover, this method can avoid the embarrassment of irreversible damage to adjacent tissue structures and 'heat sink effect'.[4] TTFields interferes with the mitosis of tumor cells by applying an alternating current electric field to the tubulin of proliferating cancer cells, thereby causing apoptosis of cancer cells and inhibiting tumor growth.[5] Compared with traditional treatment methods, TTFields has fewer side effects, and its efficacy has been clinically verified.[6]

In addition to directly inhibiting and killing tumor cells, ES therapy can also positively affect tumor immune microenvironment (TIME). ES improves immune response by regulating endogenous cytokines and enhancing the function of immune cells.[7] Consequently, the use of immunotherapeutic drugs can be reduced while simultaneously improving their efficacy in cancer treatment. However, these methods generally require continuous and stable electrical signal output through the use of complex equipment in the actual treatment process, which limits their usage scenarios and applicable tumor types. The development of electronic technology and nanomaterials has provided new ideas for tumor ES therapy. In particular, self-powered devices capable of converting energy from the environment and the human body into electrical energy for tumor treatment have been developed. Based on various electrically responsive nanomaterials, external stimuli like electricity, ultrasound and light can lead to electron-hole migration in nanomaterials, disrupting the redox homeostasis of cells and ultimately inhibiting tumor growth.[8]

In this review, we first outline the various effects of different ES on tumor cytoskeleton, cell membrane, subcellular structures as well as TIME and various cytokines (typical works are listed in Table 1) and summarized the involved signaling pathways. Subsequently, the development of carries for applying electrical signals is presented, such as nanomaterials and self-powered devices. Finally, we summarize and discuss the limitations and possible future development directions of ES therapy for tumors.

2 | EFFECT OF ES ON TUMOR AND TIME

2.1 | Effect of ES on tumor cytoskeleton

TTFields have emerged as a promising therapeutic approach that harnesses low-intensity (1–5 V/cm),

TABLE 1 The ES parameters and mechanism of action.

Electricity	Waveform	Field intensity	Frequency	Targeted cells	Mechanism	Ref.
TTFields	Sin	1–1.4 V/cm	100 kHz	GBM-glioblastome	Inhibition of mitosis	[9]
TTFields	Sin	1–3 V/cm	100–500 kHz	U-118MG, LN-18	Inhibition of DNA damage repair mechanisms by radio- or chemo-Therapy	[10]
ES	DC	0.75–1 V/cm	/	Endothelial cells	Increasing secretion of IL-8 and VEGF by endothelial cells	[11]
ES	DC	2 V/cm	/	Fibroblast, HUVECs	Induction of FGF2 secretion and increasing VEGF	[12]
ES	DC	2 V/cm	/	VEC	Inhibition of mitosis	[13]
ES	Pulse	0.6 V	80 kHz	Macrophage	Promotion of M1 polarization and inhibition of M2 polarization	[14]
ES	Pulse	500 V/cm	/	DCs	Promotion of DCs maturity	[15]
μsPEFs	Pulse	0.5–1 kV/cm	/	4T1	Mitochondrial damage	[16]
μsPEFs	Pulse	1.5–3 kV	/	TRAMP-C6	ICD-immune cell death	[17]
μsPEFs	Pulse	2.5 kV/cm	/	U251	Irreversible electroporation	[7]
nsPEF	Pulse	6 kV/cm	/	HCT-116	Membrane permeabilization	[18]
nsPEF	Pulse	7 kV/cm	10 Hz	CT-26, EL-4	ER STRESS, ICD	[4]
nsPEF	Pulse	50 kV/cm	600 Hz	U937, CHO-K1	Lysosomes disruption and autophagy induction	[8]
nsPEF	Pulse	300 kV/cm	/	Fibrosarcoma B10.2	Electroporation of cell membranes triggers ICD	[19]

Abbreviations: DC, dendritic cell; ER, endoplasmic reticulum; ES, electrical stimulation; ICD, immune cell death; nsPEF, nanosecond pulse electric field; TTFields, tumor treating fields; VEGF, vascular endothelial growth factor; μsPEF, microsecond pulse electric field.

medium-frequency (100–300 kHz) sine alternating-electric fields to proliferating cancer cells.[20–22] The primary target of TTFields is the mitosis phase of cancer cells, where the fields disrupt the formation of spindles in mid mitosis by inducing the dielectrophoretic effect of polar molecules on microtubule proteins,[23] thereby preventing the normal formation of the daughter cytoskeleton during tumor mitosis, leading to apoptosis and inhibition of tumor growth. TTFields also affect the late mitotic phase of cancer cells by disrupting proper positioning of the septum complex toward the midline of the late spindle,[24] leading to abnormal cell division and clearance.

Notably, the inhomogeneous electric field induced by TTFields in the tumor region further contributes to telophase/cytokinesis defects,[25] resulting in mitotic cleavage grooves and membrane blistering and interfering with microtubule protein polymerization.[26] Thereby inhibiting the birth of the daughter cytoskeleton. Additionally, TTFields invade the cancer cell genome, engendering genomic instability and promoting apoptosis. Furthermore, TTFields stimulate the production of DNA damage markers,[27] γ-H2AX foci, inhibit damaged DNA repair processes,[10,28] elicit replication stress, and heighten chromosomal aberrations. The p53 cascade[29] and reactive oxygen species (ROS) mass generation[30] induced by TTFields also instigate tumor cell death via the caspase enzyme-mediated apoptotic pathway.

2.2 | Effect of ES on tumor cell membranes

When tumor cell membranes are exposed to high-intensity (>1000 V/cm) ES, microsecond pulse electric field (μsPEF) and electrical signals with wide electrical pulse widths directly lead to massive membrane perforation, phosphatidylserine eversion, and membrane permeabilization of tumor cell membranes, resulting in irreversible cellular damage, release of a series of damage-associated molecular patterns (DAMPs), and stimulation of body immunity via the immune cell death (ICD) pathway, triggering body immune clearance and immune memory.[31] However, this process proceeds too aggressively and not only easily causes irreversible damage to the remaining healthy cells but also risks triggering a storm of immune factors at the same time.[7]

On the other hand, if the pulse width of μsPEF is drastically reduced, so that it strides from the subtle level to the nanosecond level, the damage of nanosecond pulse electric field (nsPEF) to tumor cells will not be so violent,

nor will it instantly cause tumor cells to rupture and die, but will pierce many tiny repairable holes in the tumor cell membrane,[18] thus disrupting the equilibrium between the inside and outside of the tumor cells, inside and outside of the endoplasmic reticulum (ER) membrane of the ion concentration balance.[32] Thereby, nsPEF stimulates a series of apoptotic pathways, such as ER stress, mitochondrial stress, and lysosomal apoptosis, mainly through Ca^{2+}, a messenger, thus making the tumor cells relatively smooth in their journey toward apoptosis.[19] Sequentially reducing the intensity of ES could significantly mitigate the direct cellular harm and risk associated with this treatment modality while still preserving the beneficial perforation effect on the cell membrane. This perforation effect could potentially enhance the efficacy of targeted anti-cancer drugs, such as curcumin (CUR),[33] by facilitating their entry into tumor cells, thereby advancing anti-cancer drug delivery system (DDS).

Furthermore, some low-intensity ES has been found to affect the expression and function of certain specific proteins or receptors on the surface of cell membranes. In cardiomyocytes, it was observed that ES led to a decrease in matrix metalloproteinase-2 (MMP-2) levels, tissue inhibitors of metalloproteinase-1 (TIMP-1) and collagen levels, and an increase in phosphorylated SMAD2 and SMAD3.[34] Unfortunately, the research evidence in this area is not sufficient and we are not able to fully elaborate the detailed mechanism of action.

2.3 | Effect of ES on mitochondria

The different ES targeting subcellular structures and organelles modulate the tumor process through diverse pathways,[35] resulting in tumor growth suppression[35] and tumor cell death (Figure 1).[40]

Mitochondria are the primary suppliers of energy to cells and play a crucial role in the tumorigenesis process. It has been shown that microsecond pulsed electric fields (μsPEF, 1–5 kV/cm, 10–100 μs) did not produce a direct physiological hindrance to 4T1 tumor cells' mitochondria.[16] However, the μsPEF led to transient perturbations but significantly reduced mouse and human breast cancer cell thymic stromal lymphopoietin signaling. In the context of actin cytoskeleton depolymerization and plasma membrane permeabilization, μsPEF affected the function of the voltage-sensitive electron transport chain (ETC),[18] shifting them toward less immunosuppressive inflammatory tumor cells and even achieving tumor cell killing. A comparative study on MCF-7 and Hela tumor cells and normal tissue cells L929 and H8 revealed that continuous positive current stimulation could utilize the inductive response of cellular mitochondrial membrane potential (MMP) and self-healing ability to more significantly regulate phenylalanine (phe) release,[41] inducing a cellular response to ES. This stimulation prompts tumor cells to move more toward the apoptotic pathway, leading to the purpose of tumor growth inhibition and tumor death. In addition, the picosecond pulse electric field (psPEF, 10–100 kV/cm, 200–800 ps) with shorter pulse duration and higher pulse intensity can have a precise targeted attack on the mitochondria of Hela cells,[42] affecting the MMP, thus triggering a series of mitochondrial apoptotic events, allowing cytochrome c and apoptotic factors to be exposed to the cytoplasm and inducing tumor cells toward apoptosis.[16]

2.4 | Effect of ES on ER

ER stress is a physiological condition in which the folding capacity of the ER is overwhelmed, leading to the accumulation of unfolded or misfolded proteins within the ER lumen,[43] ER stress is triggered by various stimuli, including changes in the cellular environment, alterations in protein synthesis, and genetic mutations that affect protein folding.[44,45] By using nanosecond pulsed electric fields (nsPEF, 10–80 kV/cm, 10–100 ns) to induce ER stress, a series of effects and cellular[38] triggered by ER stress in tumor cells can selectively induce tumor cell death[4] while minimizing damage to surrounding healthy tissues, and also improve the efficacy of conventional chemotherapy and radiotherapy.[46] The induction of ER stress by nsPEF was observed in CT26 and EL-4 cells, accompanied by ICD.[4] The unfolded protein response (UPR)[47] was triggered by ES,[48] leading to the autophosphorylation of protein kinase R-like endoplasmic reticulum kinase (PERK) and subsequent activation of the PERK apoptosis signaling pathway.[4] Furthermore, nsPEF promoted the migration of ER-attached calmodulin CRT to the cell membrane, increased the production of ROS,[39] and triggered rapid phosphatidylserine externalization, leading to the production of DAMPs that attract antigen-presenting cells (APC) to induce a strong immunogenic response. Additionally, electrical signal stimulation activated the inositol-requiring enzyme (IRE1) response on the ER membrane,[31] leading to the sequential activation of several apoptosis-inducing signaling pathways,[49] including apoptosis signal-regulating kinase-1 (ASK1), mitogen-activated protein kinase kinase 4/7 (MKK4/7), and c-Jun N-terminal kinase 1/2 (JNK1/2). ER stress triggered by ES signal also induced the shedding of immunoglobulin heavy-chain binding protein (BiP) and release of ATF6,[50] which enhanced ER UPR effect and induced tumor cells toward apoptosis. The strong electric field of nsPEF opened the ER membrane surface channel

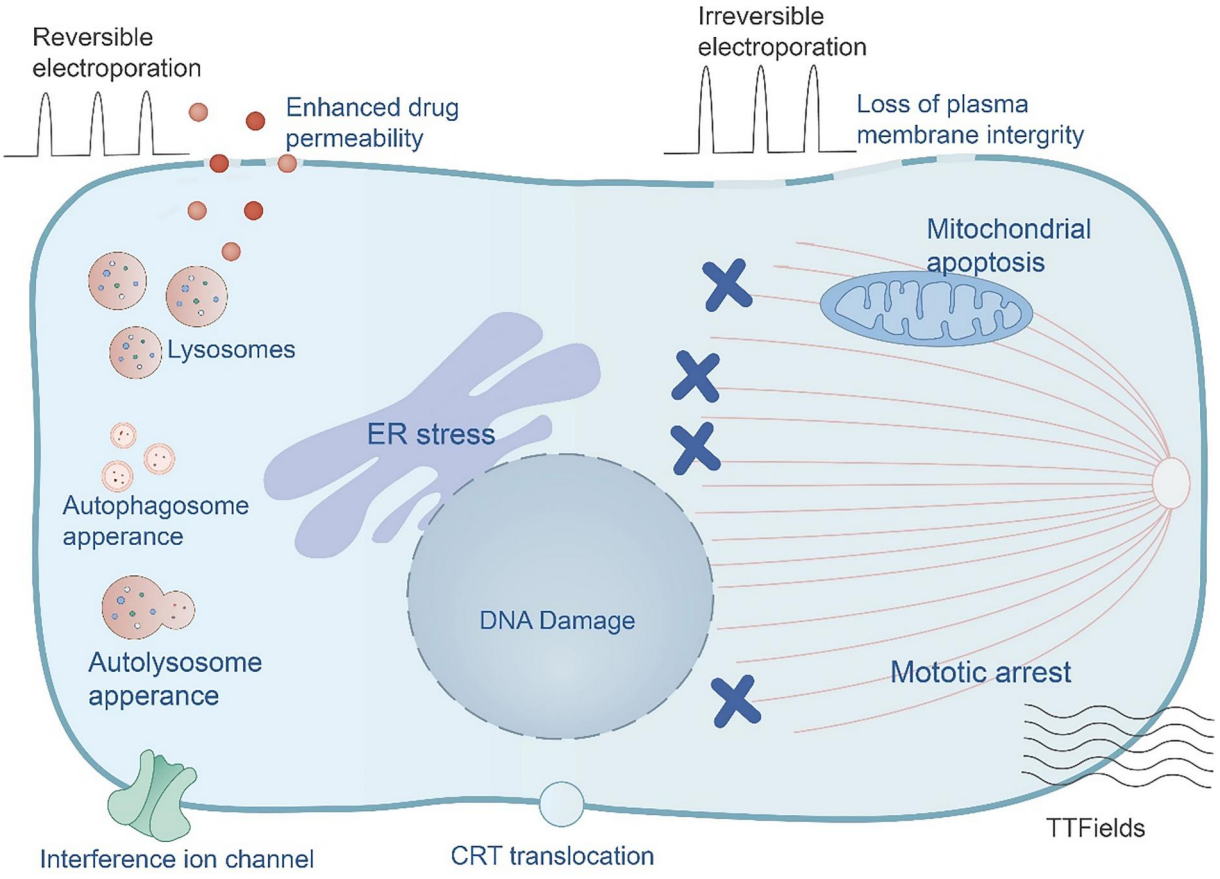

FIGURE 1 Electrical stimulation-induced modulation of subcellular structures in tumor cells. Reversible and irreversible electroporation triggers phosphatidic acid amide outgrowth by altering the permeability of tumor cell membranes, which can increase the efficiency of drug delivery[33] and activate the autolysosome pathway, the autophagic pathway and the mitochondrial apoptotic pathway,[36,37] triggering endoplasmic reticulum stress,[38] prompting CRT exposure[39] and inducing immune cell death.[31] Tumor treating fields, on the other hand, act mainly to block spindle formation at mid-cell division. Inhibits tumor cell division[24] and suppresses the operation of DNA damage repair mechanisms.[10]

proteins ryanodines receptor (RYR) and inositol-1,4,5-triphosphate receptor (IP3R), leading to a rapid outflow of Ca^{2+} from the ER to the cytoplasmic stroma,[51] followed by a large amount of extracellular Ca^{2+} influx into the cytoplasmic stroma via VDC, leading to an increase in intracellular Ca^{2+} concentration and subsequent induction of tumor cells toward the caspase apoptosis pathway.[52]

2.5 | Effect of ES on lysosomes and autophagosome

NsPEF-induced perforation of the cell membrane can lead to disturbances in the osmotic pressure balance inside and outside tumor cells,[53] and nsPEF can trigger tumor autophagy mechanisms while disrupting lysosomal repair functions,[8] presenting as increased expression of molecular markers of early, intermediate and late stages of cellular autophagy,[54] ultimately maintaining to bring cells toward apoptosis. In addition, nsPEF experiments conducted were found to avoid the formation of plasma membrane holes with little thermal effect. Jurkat, 3T3, and HL-60 cells exposed to nsPEF were observed to bind membrane coupling protein-V-FITC, subsequently absorb EthD-1, release Cytochrome C (CytC) into the cytoplasm, and activate caspase.[55] Membrane-linked protein-V binding was rapid and irreversible. nsPEF was found to initiate mitochondria-dependent apoptotic mechanisms, with 3T3 tumor cells initiating apoptosis via the p53 pathway, while Jurkat and HL-60 cells gradually moved toward apoptosis and necrosis mainly due to damage to the plasma membrane ion pump, disruption of K^+, H^+, and Ca^{2+} homeostasis,[32] and blocked cellular regulation of pH and cell signaling by blocking the lysosomal compensation mechanism. Thus, the results showed that over 30% of the cells underwent cell death following nsPEF treatment.[55]

In the context of glioblastoma (GBM), TTFields treatment activates the autophagic pathway through the

miR-29B-Akt2-mTOR axis.[36,37] Notably, RNAi inhibition of Beclin1 and autophagy-related gene 5 (ATG5) has suggested that TTFields stimulation incites GBM cells to shift to the death pathway via autophagy. Nevertheless, it has been shown that increased levels of autophagic flux in TTFields-treated cells are not associated with reduced mTOR activity in the U87MG cell line, and inhibition of autophagy sensitizes tumor cells to TTFields treatment,[54,56] leading to elevated apoptotic cell death. This suggests that autophagy in the U87MG cells line is a mechanism of resistance to TTFields.[57] Furthermore, while autophagy inhibits early-stage tumors, it is crucial for tumor cells to resist chemical and radiation attacks.[58]

Overall, pulse ES has shown significant promise in modulating subcellular structures and organelles, particularly mitochondria and ER, leading to diverse effects on the tumor process. Further investigations into the underlying mechanisms and potential therapeutic implications of ES-induced modulation of subcellular structures in tumor cells are warranted.

2.6 | Effect of ES on the TIME

The TIME comprises a complex and dynamic milieu of immune and non-immune cells, extracellular matrix components, and signaling molecules, which can either promote or inhibit tumor growth and progression.[59] One potential strategy to modulate the TIME and improve cancer treatment outcomes is low-intensity ES, which involves the application of an electric current to a tissue or organ to influence cellular behavior and physiological processes. Previous studies have demonstrated the effect of different ES on T cells, dendritic cells (DCs), macrophages, endothelial cells, fibroblast, tumor vessels, and various cytokines, which play a crucial role in tumor immune surveillance and response.

Recent findings suggest that local electrical signals generated by piezoelectric β-phase polyvinylidene fluoride (β-PVDF) films induce a significant influx of Ca^{2+} through voltage-gated channels, promoting macrophages polarization and a pro-inflammatory response.[14] Via ICD and increased DMAPs, this effect can be attributed to the regulation of Ca^{2+} concentrations in the TIME by ES, which can promote T cell immune responses and regulate the activities of immune cells and tumor cells for tumor growth inhibition and treatment. In addition, non-invasive cancer treatment modalities TTFields have shown promising effects in promoting dendritic cell phagocytosis and activation, T cell proliferation, and T cell-mediated anti-tumor immune responses and have been demonstrated to synergistically enhance the effect of anti-PD-1 therapy.[60] In addition, it has been shown that DCs become more immunogenic to tumors and mature faster when stimulated at kilovolt levels, but the high-intensity ES also poses a survival threat and causes about 20% of DC cell death.[15] It was demonstrated that a low intensity voltage of 0.6 V, by controlling Ca^{2+}-gated voltage-gated channels via the Ca^{2+}-CAMK2A-NF-κB axis, can promote the release of TNF-α and IL-1β, thus polarizing macrophages toward the inflammation-associated M1 type.[14]

Furthermore, ES can disrupt the intracellular Ca^{2+} gradient of tumor cells, inhibit the eNOS/NO pathway, prevent endothelial cell migration and differentiation, and promote tumor vessel normalization.[61] Collectively, these findings suggest that appropriate electrical signal stimulation in the TIME can modulate immune responses and Ca^{2+} signaling,[62] leading to tumor growth inhibition and improved cancer treatment outcomes. Moreover, several studies have investigated the impact of ES on various aspects of the TIME, including angiogenesis, inflammation, and immune response. Low-intensity ES has been shown to stimulate angiogenesis in the TIME, which may be mediated by the upregulation of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF),[63] or the activation of endothelial cells.[11,64] However, the optimal parameters for ES-induced angiogenesis remain to be determined, and further studies are needed to clarify the underlying mechanisms.

Low-intensity ES can also modulate the inflammatory response in the TIME by reducing the production of pro-inflammatory cytokines, such as TNF-α and interleukin-6 (IL-6), and increasing the expression of anti-inflammatory cytokines,[65] such as interleukin-10 (IL-10). These effects may be due to the activation of regulatory T cells or the inhibition of pro-inflammatory immune cells,[17] such as macrophages. Furthermore, low-intensity ES can enhance the anti-tumor immune response by increasing the infiltration and activation of immune cells, such as T cells and natural killer cells (NK cells), in the TIME.[7] This effect may be mediated by the upregulation of immune checkpoint molecules, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or the inhibition of immunosuppressive cells, such as T regulatory cells (Treg cells).[13]

ES has been extensively used as a therapeutic tool in various fields of medicine due to its ability to modulate biological processes. However, its efficacy is often limited by the commercial devices or the need for new nanomaterials. To overcome these limitations, researchers have explored all kinds of new materials and devices such

as piezoelectric nanomaterials, photoelectric nanomaterials, pyroelectric nanomaterials, nanogenerators (NG) and galvanic cells for the purpose of cancer therapy. These materials and devices are described in detail below.

3 | CELLULAR SIGNALING PATHWAYS AFFECTED BY ES

ES has emerged as a promising strategy for modulating tumor cell pathways and improving cancer therapy. ES has been shown to impact crucial pathways, including the phosphatidylinositol-3-kinase (PI3K)/AKT, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), and nuclear factor kappa-B (NF-κB) signaling pathways,[23] which play critical roles in tumor cell proliferation, survival, and metastasis (Figure 2).

3.1 | Effect of ES on PI3K/AKT pathway

The PI3K/AKT pathway plays a crucial role in cell proliferation, differentiation, and survival, making it an attractive target for cancer therapy. After the calcium channel protein TRPV4 is stimulated by electrical signals,[67] the calcium concentration in tumor cells decreases, the PI3K/AKT pathway is inhibited,[68] and tumor cell growth and proliferation are slowed. Furthermore, it was demonstrated that EFs stimulate eNOs activation and NO production via PI3K/Akt-dependent

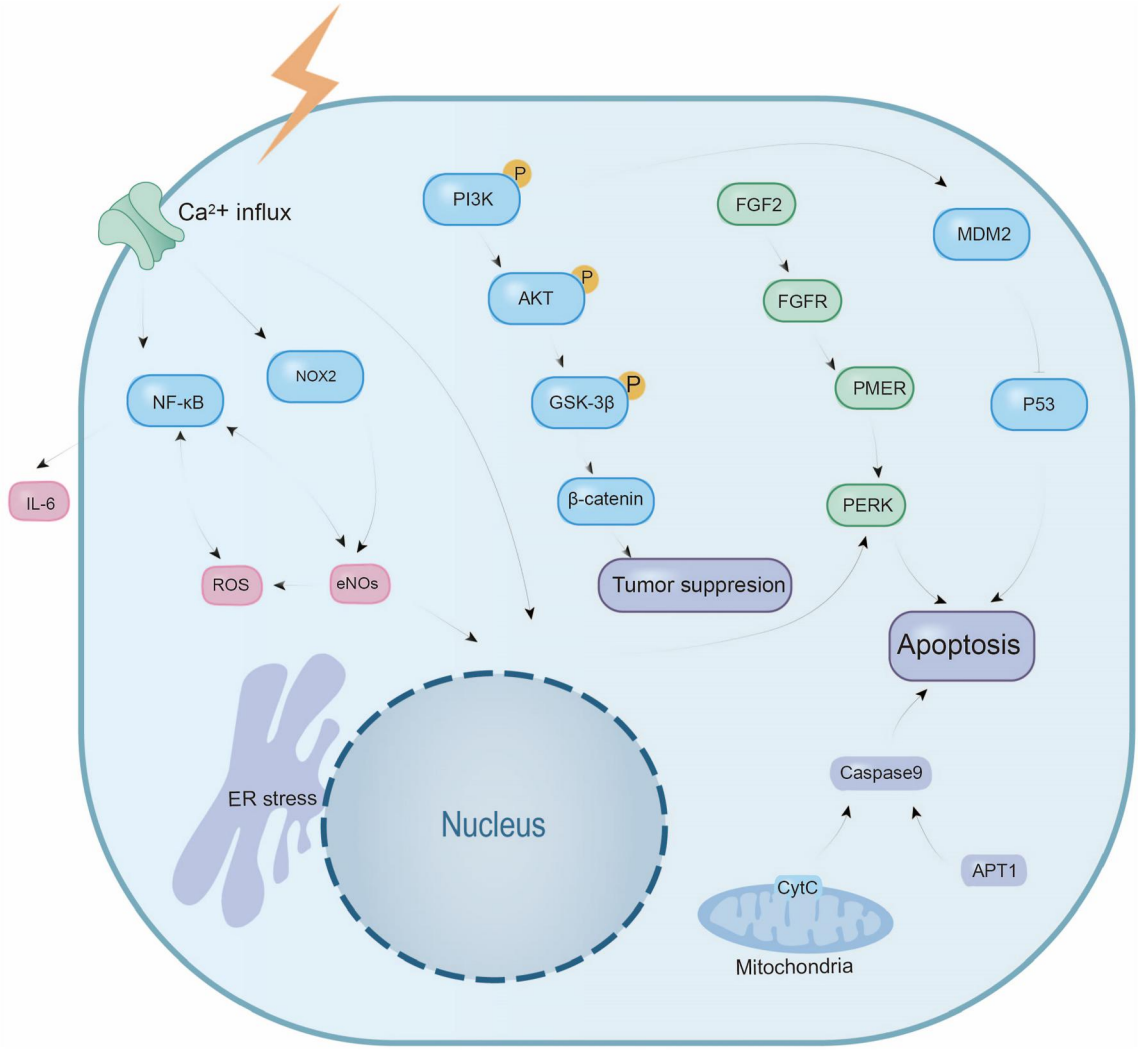

FIGURE 2 Effect of ES on tumor cell pathways. ES activates NF-κB signaling[23] by regulating intracellular Ca^{2+} signaling,[19] triggers ROS and eNOs stress effects,[30,66] and triggers ER stress; ES inhibits tumor cell progression via PI3K/AKT pathway[67,68]; ES drives tumor cells toward apoptosis via PERK and p53-related pathways[4,29,32]; ES triggers MMP disturbance, releases CytC, and activates caspase 9 apoptosis pathway.[41,55] CytC, cytochrome C; ER, endoplasmic reticulum; ES, electrical stimulation; MMP, mitochondrial membrane potential; NF-κB, nuclear factor kappa-B; ROS, reactive oxygen species.

pathway, inducing significant phosphorylation of eNOs, upregulation of eNOs protein expression, and increased NO production in HUVECs, promoting angiogenesis.[66]

3.2 | Effect of ES on MAPK pathway

The MAPK pathway is a highly conserved signaling pathway that regulates various cellular processes,[69] including cell proliferation, differentiation, and apoptosis. The MAPK pathway consists of a cascade of protein kinases that are activated in response to extracellular signals, including growth factors, cytokines, and stress. The MAPK pathway is divided into three main subfamilies: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK. Application of nsPEF to HeLa S3 cells induced the phosphorylation of MAPKs, including p38, JNK and ERK,[12] and their upstream kinases. The application of nsPEF also elicited elevated phosphorylation of downstream factors, including MSK1, Hsp27, ATF2, p90RSK, and c-Jun. In addition, the application of nsPEF led to the transcriptional activation of immediate early genes in the MAPK pathways.[70] Treatment with inhibitors of the MAPK pathways suppressed nsPEF-induced protein phosphorylation and gene expression downstream of MAPKs,[71] confirming the functional connection between the nsPEF-activated MAPKs and the observed induction of the downstream events. TTFields can also induce RAW264.7 macrophages and activate the NK-κB/MAPK signaling pathways.[72]

3.3 | Effect of ES on NF-κB pathway

NF-κB has long been known to function as a critical regulator of apoptosis and often induces genes favoring cell survival; these gene products include cellular inhibitors of apoptosis (CIAPs), BCL2s, TRAF1/TRAF2, and superoxide dismutase (SOD). NF-κB can also modulate the expression of apoptosis-promoting cytokines such as tumor necrosis factor-alpha (TNFα) and FAS ligand (FASL).[73] Microsecond pulsed electric fields can alter single gene expression in the plasmid environment of various cell lines without causing significant damage to cell integrity or viability, and by modulating ES parameters, the expression of NF-κB promoter-controlled genes can be up-regulated and down-regulated.[74] In addition, it has been shown that depolarization-induced increase in intracellular Ca^{2+} and ROS production are necessary for NF-κB activation, and ES can induce ROS production, increase NADPH oxidase expression, trigger Ca^{2+} release, thereby activating the NF-κB pathway and affecting IL-6 expression.[75] It has been demonstrated that, in conjunction with encoding L-type voltage-gated calcium channels, μsPEF can upregulate the NFAT promoter-controlled SEAP gene expression system in HEK-293T cells, while affecting the study of cytoplasmic membrane fluidity and cytoskeletal state, thereby triggering the NF-κB pathway.[76]

Overall, ES represents a promising strategy to target multiple tumor cell pathways and improve cancer therapy, but the detailed mechanism by which ES acts on tumor cell pathways remains to be uncovered.

4 | SELF-POWERED DEVICES FOR THE ES

Traditional commercial power supply for ES therapy used in clinical practice has high energy consumption and maintenance cost. Besides, the waste battery will have a bad impact on the environment. The emergence of new technologies, such as nanogenerators, have broken the limitations of traditional technologies and injected fresh blood into cancer therapy.

4.1 | NG as a power source for the cancer therapy

In the past decade, piezoelectric nanogenerator (PENG)[77] and triboelectric nanogenerator (TENG),[78] which were invented by Z. L. Wang, have developed rapidly. The basic principle of TENG is as follows: the electrostatic charge is generated when the surfaces of two different materials are physically in contact. After separating the surfaces of two materials under mechanical force, the contact-induced frictional charge can produce a potential drop, which will drive the flow of electrons between two electrodes on the top and bottom surfaces of two materials. There are currently four basic modes of TENG: vertical contact-separation mode, lateral sliding mode, single-electrode mode and freestanding triboelectric-layer mode. Due to their low fabrication cost, portability, and the ability to extract energy from mechanical vibration (such as human motion), the self-powered nanogenerators have a wide range of applications in the medical and health fields.[79–81]

At present, in the field of tumor therapy, NGs are mainly used as an energy supply source to stimulate drug release.[82–84] Zhao et al. designed a new magnetic TENG (MTENG) to control the release of DOX from red blood cells (RBC) loaded with DOX (D@RBCs).[82] The two friction layers of this MTENG are made of polytetrafluoroethylene (PTFE) with nanostructures on the

surface, to increase contact area and consequently triboelectric output, and titanium (Ti). On the back of each friction layer, a Cu film was sputtered to be used as electrode. MTENG was encapsulated with Polydimethylsiloxane (PDMS) to protect it from harsh environments (Figure 3a). Since the tendency of separation between two friction layers became smaller after being encapsulated or having a long-time operation, the TENG showed a decreased output. In this work, the lifetime of the MTENG was guaranteed by assembling a pair of magnets on the TENG. The MTENG could collect mechanical energy in the environment to generate an electric field. The generated electric field could stimulate the formation of nanopores on the membrane of RBC, which led to a significant increase in DOX release (Figure 3b). When the electric field stimulation stopped, the release of DOX returned immediately to the basal levels. Limited to the intricate implantation site and environment, the MTENG cannot be implanted. Late in 2022, the same group prepared an implantable TENG (iTENG), which used the same materials as MTENG but changed shapes for circle, rectangle, square, and rhombus.[83] It was well matched with the internal tissue in terms of shape and size. This RBC-based implanted DDS with iTENG could be used to precisely control the release of chemotherapeutic agents from APA-loaded RBC (A@RBC). This led to a good killing effect on tumor cells in vivo and in vitro. When the DDS was implanted into the rabbits, it showed anti-tumor effect in situ.

In addition to chemotherapeutic agents, TENG has also been used to stimulate the release of therapeutic gases. Yao et al. designed a wearable, stretchable TENG

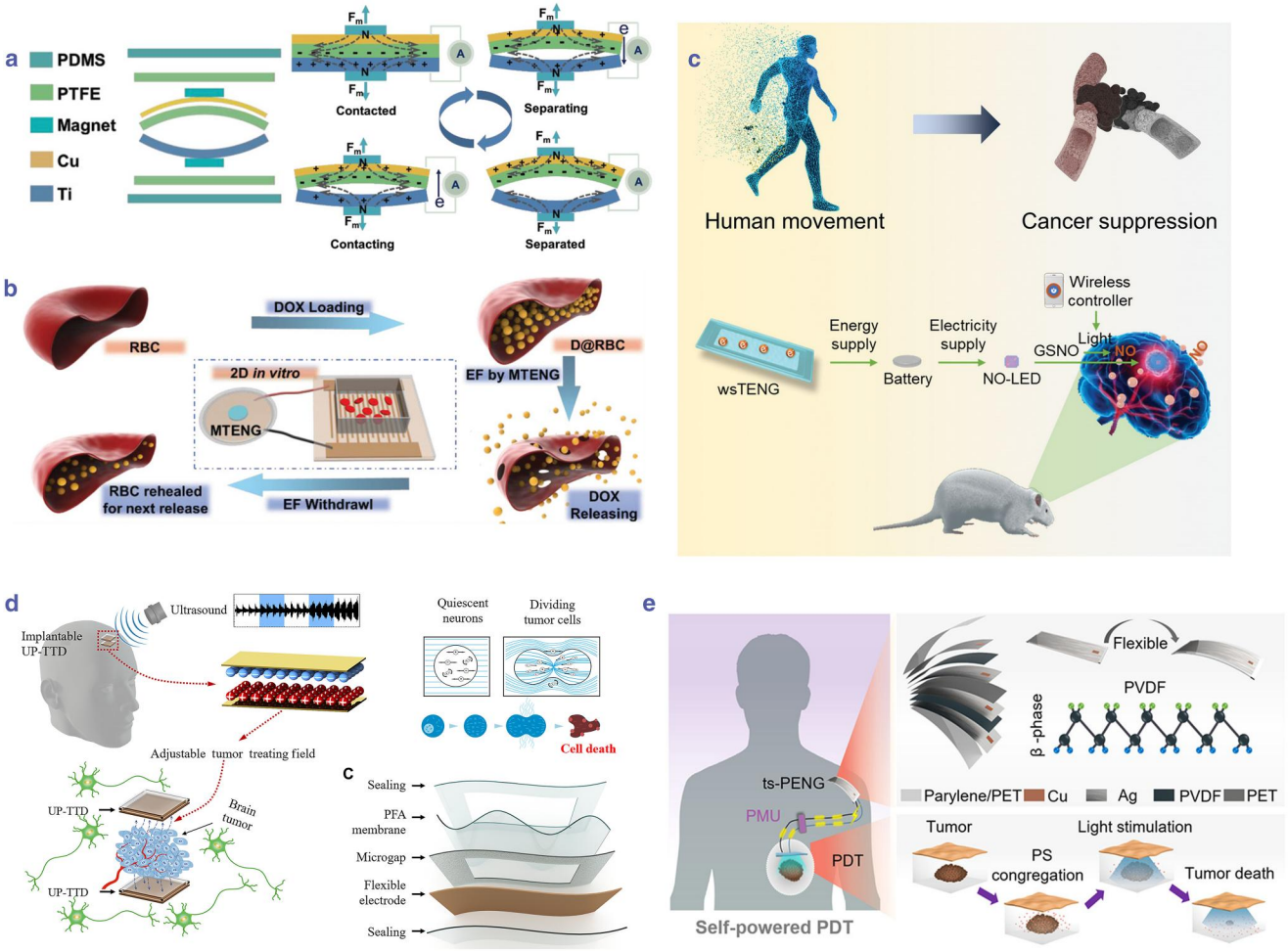

FIGURE 3 (a) Composition and working principle of MTENG. Reproduced with permission. (b) Schematic diagram of MTENG controlling the release of DOX from D@RBCs. Reproduced with permission.[82] Copyright 2019, Wiley-VCH. (c) NO gas-therapy system based on self-powered wsTENG for intracranial glioblastoma therapy. Reproduced with permission.[85] Copyright 2022, Wiley-VCH. (d) The structure of UP-TTD and its mechanism of tumor therapy. Reproduced according to the terms of the CC-BY license.[86] (e) The structure and composition of s-PDT system and the process of inducing apoptosis in subcutaneous tumor tissue. Reproduced with permission.[87] Copyright 2020, American Chemical Society. MTENG, magnetic TENG; UP-TTD, ultrasound-driven tumor therapy device; wsTENG, wearable, stretchable TENG.

(wsTENG) with single-electrode mode.[85] The wsTENG could be attached to human body to collect energy from movement (Figure 3c). A NO releasing device (NO-LED) implanted transcranial close to tumor tissue was powered by the generated energy from wsTENG. When the LED was lit by the wsTENG, the device released NO for gas therapy sustainably. What's more, the current generated by TENG can also act directly on tumor cells. Chu et al. found that when the stimulating current generated by TENG was 150 μA, the actin and tubulin-associated cytoskeleton would be disrupted, thereby inhibiting cell migration in vitro. Moreover, the tumor metastasis was effectively inhibited in mice with 4T1-LUC tumor metastasis model.[88] In addition, Xu et al. prepared an implantable ultrasound-driven tumor therapy device (UP-TTD) based on TENG (Figure 3d). Under ultrasound, the perfluoroalkoxy (PFA) film in the device generated a microdisplacement, which produced the electrical output through contact with adjacent metal electrodes. The generated alternating electric field could interfere with the rapid division of cancer cells without any adverse effects on normal neurons, and thus safely inhibited brain cancer recurrence.[86]

In addition to TENG, PENG can also be used for energy supply. Liu et al. designed a wearable twinning structure piezoelectric nanogenerator (ts-PENG) for cancer therapy[87] (Figure 3e). The ts-PENG was encapsulated by Parylene-C and could convert the energy generated by joint motion into electrical energy to drive the PDT system. By designing a power management unit (PMU), two modes of irradiation could be achieved: pulsed light stimulation (PLS) and intermittent continuous light stimulation (ICLS). Intermittent, low-dose PLS stimulation could inhibit the growth of tumor cells by up to 60%. After 12 days of irradiation under ICLS mode, the tumor inhibition rate was 87.46%. Compared with other PDT devices, this PDT system based on ts-PENG could avoid the adverse reactions caused by excessive PDT exposure and improve the safety and reliability. And the implantability of ts-PENG expanded its application in the biomedical field.

4.2 | Galvanic cell for the cancer therapy

Galvanic cell is a device that can generate electric energy through redox reactions in aqueous spontaneously. In an electrolyte solution, the reducing agent loses electrons on the negative electrode for oxidation reaction, followed by the transportation of electrons to the positive electrode through the external circuit. The oxidant obtains electrons on the positive electrode for reduction reaction, thus completing the transfer of electrons between the reducing agent and the oxidant. The directional movement of ions in the solution between the two poles and the directional movement of electrons in the external wire constitute a closed loop. So that the reaction of two electrodes continues, an orderly process of electron transfer occurs with the generation of current. Finally, the conversion of chemical energy to electric energy is realized. Based on this principle, Yang et al. designed a micro-galvanic cell based on in situ reduction of a small number of platinum (Pt) nanoparticles on the surface of Mg rods. The galvanic cell can produce H_2 gas and Mg $(OH)_2$ in water through redox reaction (Figure 4a).[89] After being implanted into the tumor (Figure 4b), the production of H_2 was sustained, which inhibited mitochondrial respiration and disrupted redox homeostasis within the tumor cells. In addition, the generated Mg $(OH)_2$ could regulate the acidic ITME and promote the transformation of immune-suppressive TIME into immune-promoting TIME, which is beneficial to antitumor therapy.

In addition to gas generation, galvanic cell can also consume gas. Huang et al. prepared a self-powered battery using polyimide electrodes and zinc electrodes as positive and negative electrodes, respectively.[90] On the one hand, the battery would consume oxygen in the tumor site and generate oxygen free radicals, which prevented the formation of tumors. On the other hand, oxygen consumption aggravated oxygen-depleted environments at tumor sites, which facilitated activation of hypoxia-activated prodrugs (HAPs) and thus killed tumor cells (Figure 4c). The combination enhanced the effectiveness of cancer treatment. The structure and composition of galvanic cells are shown in Figure 4d,e.

5 | ELECTRICALLY RESPONSIVE NANOMATERIALS

In addition to macroscopic devices, the smaller nanomaterials can also generate weak electrical signals in response to external stimulation (such as temperature, light, ultrasound, etc.). Electrically dependent stimuli-responsive nanomaterials refer to materials that exhibit specific changes in their own characteristics triggered by environmental changes,[91–93] and these changes will generate electrical signals finally. Such materials include various nanocatalysts, such as photosensitizers and sound sensitizers. Or the materials that undergo some changes under ES, such as electrocatalytic nanomaterials. Each of these materials is described below.

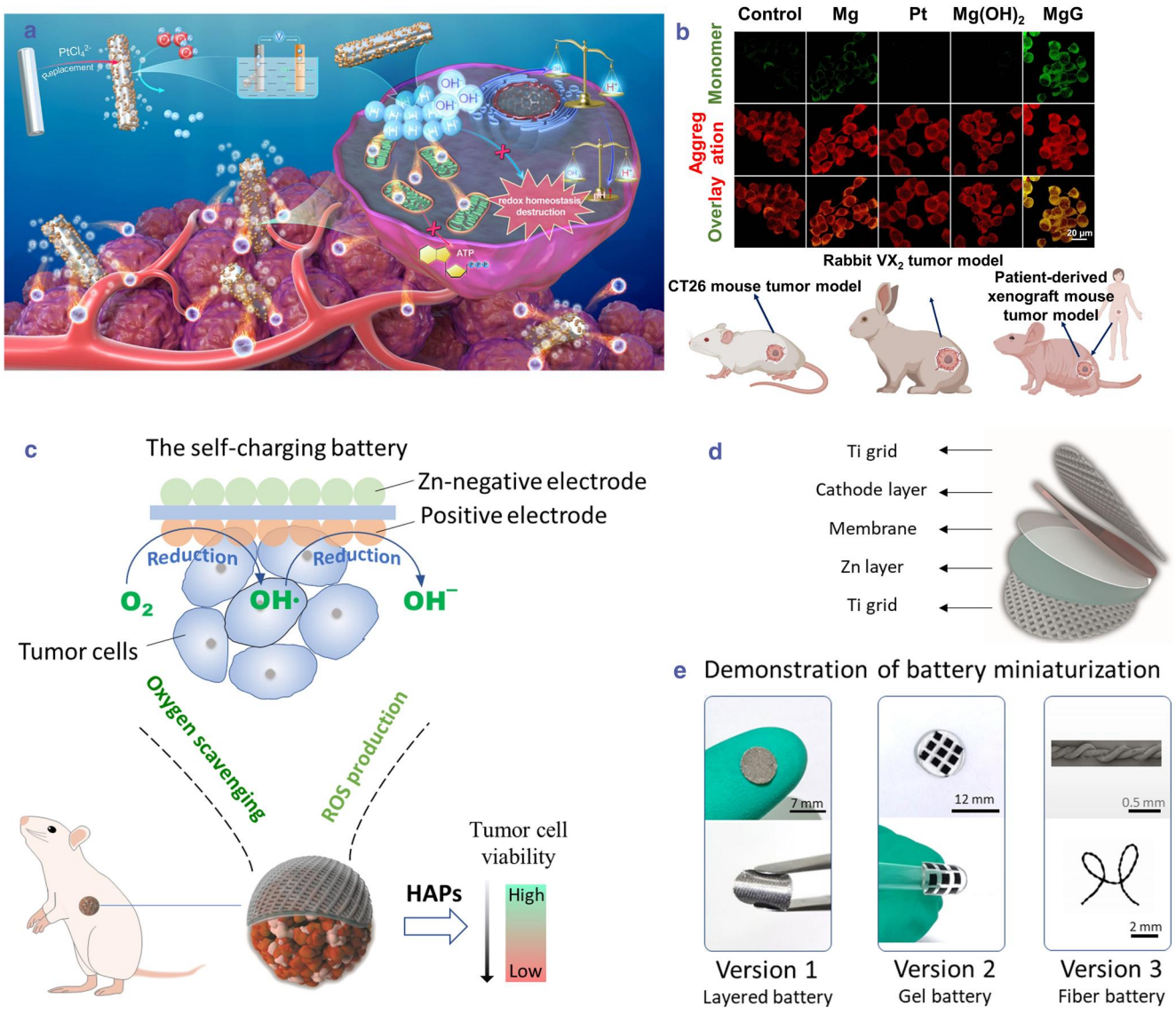

FIGURE 4 (a) Schematic diagram of the preparation of MgG for TIME regulation and enhancement of cancer hydrogen therapy. (b) Antitumor effects of MgG in vivo and in vitro. Reproduced with permission.[89] Copyright 2022, Springer Nature. Principle (c) and structure (d) and (e) diagram of a self-rechargeable battery used in tumor treatment. Reproduced according to the terms of the CC-BY license.[90] MgG, magnesium galvanic cells; TIME, tumor immune microenvironment.

5.1 | Photoelectric nanomaterials for the cancer therapy

Photosensitizer (PS) is an indispensable part in photodynamic therapy of tumors. The ROS required for photodynamic therapy are generated based on the PSs after absorbing the energy from the photon under the excitation of the light source. Firstly, the excited PSs after absorbing the photon energy will transfer into a long-lived excited state (called triplet state) through the intersystem crossing. Finally, ROS is generated by energy transfer or electron transfer. The mechanism of electron transfer to produce ROS is usually called type I reaction, while the other mechanism is called type II reaction.[94–97]

The development and progress of technology have led to an increasing variety of materials. Photoelectric nanomaterials, mainly semiconductor nanomaterials, are a class of nanomaterials that can convert light energy into electric energy. When exposed to light, electrons in the valence band of the materials will absorb the photon energy and transition to the conduction band, leaving corresponding holes in the valence band. The electron in the conduction band and the hole in the valence band are called carrier. The light can cause the change of the carrier concentration in the photoelectric nanomaterials, thus generating photocurrent. In the process of photocurrent generation, these electron-hole pairs induced in semiconductor photoelectric nanomaterials can react

with water or oxygen to produce ROS. Therefore, photoelectric nanomaterials can be used as photosensitizers for tumor therapy.

TiO_2 has attracted much attention in ultraviolet (UV)-triggered PDT due to its wide bandgap (3.0–3.2 eV), chemical stability, cost effective and low toxicity.[98] However, the penetration is limited by weak UV-vis light and the tumor therapy deep in the tissue cannot be performed. Kotagiri et al. firstly reported Cerenkov radiation (CR)-induced PDT with 2′-deoxy-2′-(^{18}F)fluoro-D-glucose (^{18}F-FDG) and ^{64}Cu as light source, semiconductor nanomaterial TiO_2 as photosensitizer. TiO_2 was modified with apo-Tf and titanocene (Tc) to achieve the purpose of enhancing the effect of targeted photodynamic therapy (Figure 5a,b).[99] Near-infrared light with deep penetration in biological tissues has low thermal effects and phototoxicity, which solves the limitation of the excitation light on PS in the UV-Vis region. Upconversion nanoparticles (UCNPs) have the fluorescence resonance energy transfer (FRET) effect of near-infrared light. Zhang et al. prepared uniform core-shell NPs with TiO_2 layer as shell, coated on the single UCNP core (Figure 5d). UCNPs can convert 980 nm light into UV light, which stimulated the formation of electron-hole pairs within TiO_2, and finally initiated redox reactions to produce ROS.[101] After surface modification with polyethylene glycol (PEG) to make it biocompatible, the nanoparticles showed good therapeutic effect both in vitro and in vivo.

In addition, the UV light excitation and rapid recombination of electrons with holes in pristine TiO_2 would result in a significant reduction in photodynamic efficiency. Modification with nanomaterials on the surface of TiO_2 can increase the separation of electrons and holes and improve the efficiency of light utilization. Yang et al. designed carbon nanodots modified TiO_2 nanotubes (CDots/TiO_2 NTs).[103] In this structure, CDots play a role in narrowing the band gap and enhancing the light absorption response. The relative position of the CDots band edges made the electrons transfer from the TiO_2 material surface, which promoted the separation of electron-hole pairs and hindered their recombination. The isolated electrons and holes can further react with O_2 and H_2O, respectively, and form $\bullet O_2^-$ and ●OH. Thus, the composite nanomaterials exhibited significantly enhanced PDT properties.

Most traditional UCNPs can't achieve programmable activation of biomolecules or drugs when excited by a single wavelength of light. Zhang et al. designed a programmable UCNP superball through a simple emulsion synthesis method (Figure 5c). The superball could be activated by 980 and 808 nm light, and finally achieve orthogonal upconversion emission. After endocytosis, the ROS generation was induced under 980 nm laser irradiation. Then, the 808 nm laser made cancer cells release siRNA for gene knockout. Finally, PDT was activated by a 980 nm laser. This programmable irradiation can make optimal gene knockout happen before PDT, which resulted in a better effect in cancer therapy.[100]

In addition to the generation of ROS for tumor treatment, photoelectrons can also affect the cellular metabolism of organisms to achieve the purpose of antitumor. Researchers have reported a light-controlled material-assisted microbial system. This Bac@Au was obtained by biosynthesizing gold nanoparticles (AuNPs) on the surface of Shewanella algae K3259 (S. algae) (Figure 5e). The in situ synthesis of anti-tumor tetrodotoxin (TTX) was promoted by the bidirectional electron transport mechanism of S. algae. Due to the tumor hypoxia targeting of facultative anaerobic S. algae, Bac@Au selectively targeted tumors. Upon exposure to light, photoelectrons generated by Au NPs on the surface of bacteria were transferred into the bacterial cytoplasm and accelerated cellular metabolism, thereby increasing TTX production for antitumor therapy.[102]

5.2 | Pyroelectric nanomaterials for the cancer therapy

In phototherapy, prolonged exposure to NIR light will cause a local temperature increase, and this temperature fluctuation generates thermal energy. Pyroelectric materials have the characteristic of spontaneous polarization that depends on temperature oscillation. The temperature change will lead to a slight spatial movement of atoms in the crystal structure, which will cause the change of internal polarization in pyroelectric materials and induce pyroelectric charge on the surface of pyroelectric materials. Finally, usable electric energy with high energy conversion efficiency and polarized charge carriers is generated. Therefore, nanomaterials with pyroelectric catalytic properties can be triggered by temperature fluctuations to generated positive and negative charges for redox reactions and achieve the purpose of generating ROS for tumor therapy eventually.

At the beginning, pyroelectric nanomaterials are often used to solve the problem of microbial contamination. Pyroelectric catalysis technology has attracted more and more attention, and its application scope has gradually expanded to the medical field. In 2018, Tang et al. synthesized SnSe-PVP nanorods with integrated high performance photothermal and pyroelectric conversion capabilities (Figure 6a).[104] SnSe-PVP nanorods with heat generated under NIR-II light irradiation killed cancer cells through PTT. In addition, the temperature

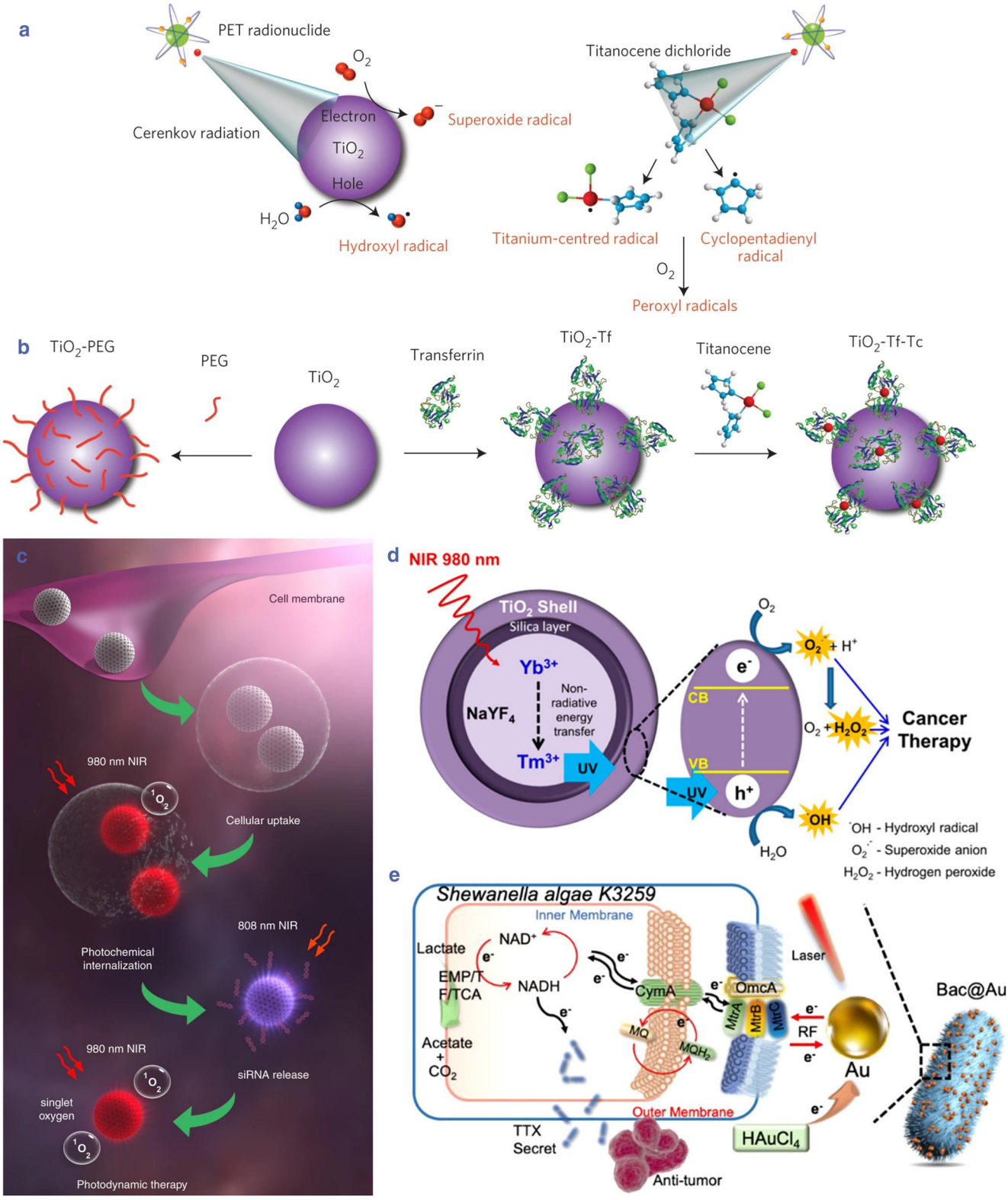

FIGURE 5 (a) The generation of radicals in TiO_2 nanoparticles and titanocene through the Cerenkov radiation-mediated excitation. (b) The modification of TiO_2 nanoparticles. Reproduced with permission.[99] Copyright 2015, Springer Nature. (c) Programmable PDT with upconversion superballs. Reproduced with permission.[100] Copyright 2019, Springer Nature. (d) The mechanism of reactive oxygen species generation by TiO_2-UCNs for tumor therapy under infrared irradiation. Reproduced with permission.[101] Copyright 2015, American Chemical Society. (e) Mechanism of enhancing tetrodotoxin production for antitumor therapy. Reproduced with permission.[102] Copyright 2021, American Chemical Society.

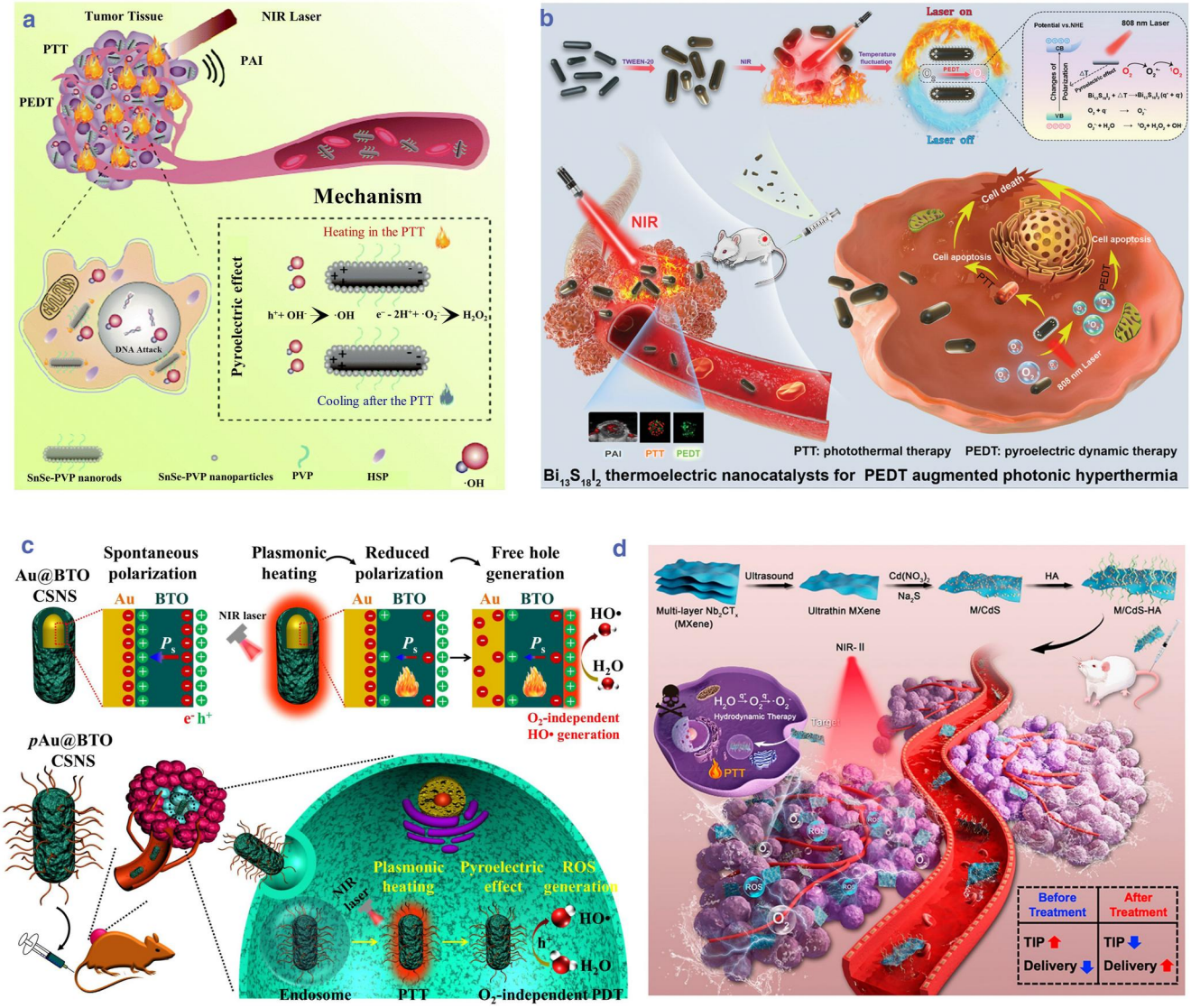

FIGURE 6 (a) Diagram of PAI and PTT with PEDT using SnSe-PVP nanorod under NIR-II laser. Reproduced with permission.[104] Copyright 2018, The Royal Society of Chemistry. (b) $Bi_{13}S_{18}I_2$ NRs converted hot–cold alterations into pyroelectric charges under the irradiation of 808 nm laser; the generated pyroelectric charges reacted with the surrounding O_2 molecules to produce many ROS. Reproduced with permission.[105] Copyright 2021, Wiley-VCH. (c) Mechanism diagram of plasmon resonance induced pyroelectric effect of Au@BTO CSNSs and generation of ROS. Reproduced with permission.[106] Copyright 2021, Elsevier Ltd. (d) Schematic diagram of pyroelectric catalysis for enhanced cancer therapy with "nano-lymphatic." Reproduced with permission.[107] Copyright 2021, American Chemical Society. NRs, nanorods; PEDT, pyroelectric dynamic therapy; ROS, reactive oxygen species.

difference during the photothermal and cooling process led to a potential difference on the surface of the SnSe-PVP nanorods. Then, the electrons generated and reacted with water to generate ROS. The obtained ROS would attack HSPs and cancer cells finally. This treatment method that exploits the pyroelectric effect is defined as pyroelectric dynamic therapy (PEDT). The pyroelectric catalytic efficiency of pyroelectric nanomaterials has influence on the effect of PEDT. Wang et al. reconstructed typical binary compounds by inserting a third biocompatible reagent to form $Bi_{13}S_{18}I_2$ nanorods (NRs) with enhanced pyro-catalytic conversion efficiency.[105] The nanorods could obtain pyro-catalytic energy from the heating and cooling process, which leads to the production of ROS and depletion of HSPs, thereby reducing the thermal resistance of tumor cells and ultimately enhancing the efficacy of photothermal tumor hyperthermia (Figure 6b).

When the pyroelectric material is exposed to a temperature changing environment, the orientation of the internal dipoles will have a change, eventually leading to the release of the screened charges (e^- or h^+). These released charges may be used to generate ROS without O_2. Therefore, Chang et al. designed a plasmon-pyroelectric

nanostructure for hypoxic tumor therapy (Figure 6c). Photothermal nanomaterial gold (Au) nanorods (NRs) were embedded in the pyroelectric material barium titanate (BTO) to form Au@BTO core-shell nanostructures.[106] Under NIR light irradiation, the LSPR-mediated photothermal properties of Au NR would increase the temperature of the BTO shell, which resulted in a decrease in the spontaneous polarization field and the release of excess screened holes on the surface of BTO shell. These holes further reacted with H_2O to generate ●OH. Combined with PTT treatment, these plasmon-pyroelectric nanomaterials could effectively inhibit tumor growth. Considering that pyroelectric nanomaterials can react with H_2O during catalysis, and the retention of tumor interstitial fluid leads to increased tumor interstitial pressure (TIP), which limits the penetration of nanomedicine. He et al. designed a 'nanolymphatic' based on pyroelectric catalysis to achieve tumor interstitial fluid decomposition and generation of ROS under NIR II irradiation (Figure 6d). The reduced TIP would enhance the penetration of nanomedicine. At the same time, ROS generated during pyroelectric catalysis caused damage to deep cancer stem cells.[107]

5.3 | Piezoelectric nanomaterials for the cancer therapy

Most FDA-approved photosensitizers respond to UV or visible light and have strong phototoxicity. However, the low penetration depth of UV or visible light limits the application. Compared with light, ultrasound can penetrate deep tissue. Therefore, the piezoelectric materials attract more and more attention.[108]

Piezoelectric materials can promote the conversion of mechanical into electrical energy. When the pressure, tangential force, or tension is applied, the center of positive and negative charges inside the piezoelectric material is displaced. Then, the charge is generated on both the upper and lower surfaces of the material, and the charge density is proportional to the applied mechanical force. This conversion of mechanical energy into electrical energy is called the positive piezoelectric effect. When the piezoelectric material is subjected to an external electric field, the crystal will deform. This conversion of electrical energy into mechanical energy is known as the inverse piezoelectric effect. The piezoelectric effect can induce interfacial charge transfer, which leads to a good redox catalytic activity (Figure 7a).[109] Under the action of mechanical stimulation, the electron-hole pairs generate within the piezoelectric materials and then the redox reaction occurs.[113] The combination of ultrasound and piezoelectric materials is widely used in biomedicine such as tumor treatment because of its ability to penetrate deep tissues with minimal trauma.

At present, the mechanisms of mechanical stimulation of piezoelectric nanomaterials for tumor treatment are mainly as follows: (1) Catalyzing the generation of ROS, thereby killing cancer cells. (2) Generating electrical signals to affect biological activities, thereby promoting the apoptosis of cancer cells. BTO is a wide-band gap ferroelectric semiconductor, while tetragonal BTO (T-BTO) is a typical piezoelectric material. Polarization occurs inside T-BTO under pressure, which will lead to the separation of internal electron-hole pairs and then catalyze the redox reactions. Shi et al. firstly combined ultrasound with T-BTO piezoelectric nanoparticles for tumor therapy (Figure 7b). T-BTO could generate polarization under US and produced a higher internal electric field, which effectively promoted the production of ROS and could effectively kill tumor cells.[110]

There are often pathological blood vessels in tumor tissues, which lead to local hypoxia, affect the efficiency of blood transport, hinder drug transport and the therapeutic effect on tumors. Inspired by the intervention of endogenous bioelectricity in angiogenesis,[114] Li et al. designed a tetragonal polarized BTO that could generate pulsed open-circuit voltage under the low-intensity pulsed US. The voltage inhibited the endothelial cell migration and differentiation as well as eNOS/NO pathway related to angiogenesis in vitro. What's more, ES generated by nanoparticles could optimize vascular structure, restore local oxygenation and normalize tumor blood vessels (Figure 7c).[111]

Piezoelectric potential can not only promote vascular normalization but also influence other physiological activities. For example, Ma et al. designed a US activated tumor treatment platform based on Au/ZnO (Figure 7d). Under US stimulation, ZnO nanogenerators could generate about 140 mV piezoelectric potential difference. The potential difference could destroy mitochondrial membrane potential and enhance the enzyme-like activities of Au, which can be used for catalytic treatment of tumor.[112]

5.4 | Electrocatalytic nanomaterials for the cancer therapy

EChT involves the insertion of electrodes at or around the center of solid tumors to locally induce destructive electrolytic reactions by introducing low-voltage direct current (DC).[115] Compared with other systemic therapies, EChT is relatively inexpensive, destroys relatively localized areas, and results in fewer side effects. However, it does harm to not only tumor cells but also normal cells.

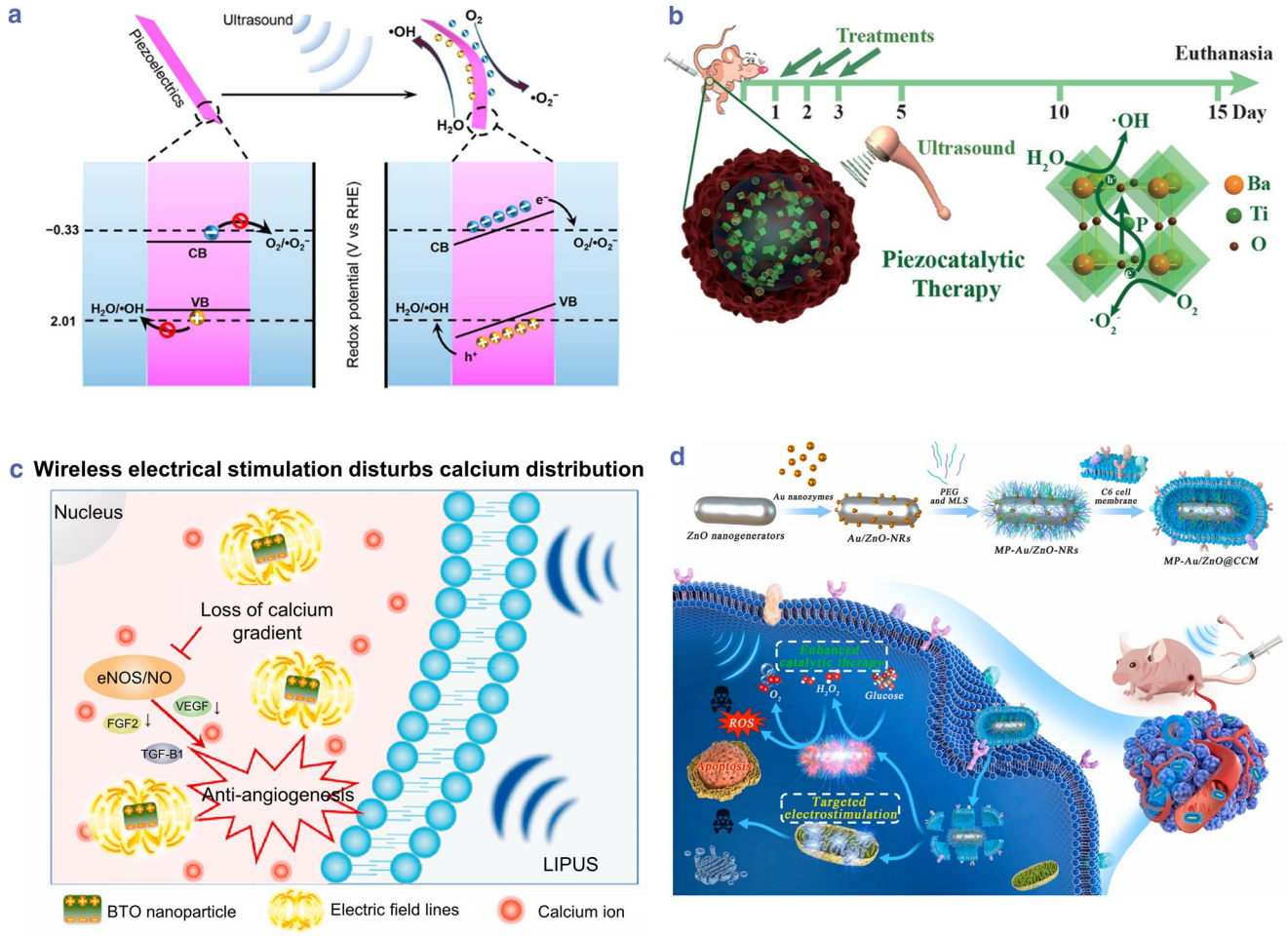

FIGURE 7 (a) The piezoelectric polarization of the piezoelectric materials under the US, which can generate ROS through the redox reaction. Reproduced with permission.[109] Copyright 2020, American Chemical Society. (b) Schematic illustration of piezocatalytic therapy in vivo. Reproduced with permission.[110] Copyright 2020, Wiley-VCH. (c) Schematic diagram of BTO nanoparticles modulating angiogenesis under low-intensity pulsed US. Reproduced according to the terms of the CC-BY license.[111] (d) Schematic illustration of the synthesis and enhanced catalytic treatment of MP-Au/ZnO@CCM Trojan nanogenerators. Reproduced with permission.[112] Copyright 2021, Elsevier Ltd. BTO, barium titanate; ROS, reactive oxygen species.

In addition, the therapeutic efficacy and procedural difficulty of EChT are constrained by the shape and size of the tumor.

Liu et al.[116] used nanoparticles with electrocatalytic function to catalyze the reaction. The electrically driving platinum nanoparticles (Pt NPs) under square wave AC could generate cytotoxic hydroxyl radicals, then the tumor cells within the entire electric field would be effectively killed (Figure 8a). Moreover, this process of ROS production was not affected by the hypoxic TIME. This approach that induces the generation of ROS by nanoparticles driven under an oscillating electric field has been termed electrodynamic therapy (EDT). The nanomaterials used for EDT possess electrocatalytic property. To further improve the efficacy of EDT, the research group modified platinum nanoparticles to load chemotherapy drugs.[119,120] By combining EDT with chemotherapy, its anti-tumor effect was enhanced. In addition to chemotherapeutic drugs, Han et al. synthesized porous platinum nanospheres (pPts) conjugated to GOx molecules (PtGs) to achieve oxygen-inductive starvation/EDT synergistic treatment strategies.[121] GOx could catalyze the oxidation of glucose and produce H_2O_2. pPts triggered the decomposition of H_2O_2 and produced a large amount of O_2 to facilitate glucose consumption by GOx. At the same time, pPts induced a significant increase in intracellular ROS under an alternating electric field. The coupling of the two strategies showed significant anticancer effects.

In addition to the combination with chemotherapy to enhance the effect of tumor treatment, EDT can also be combined with other treatment methods, such as chemodynamical therapy, immunotherapy and so on. Li et al. used platinum nanocrystals to modify iron oxide nanoparticles (Fe_3O_4@Pt NPs) for the cancer therapy.

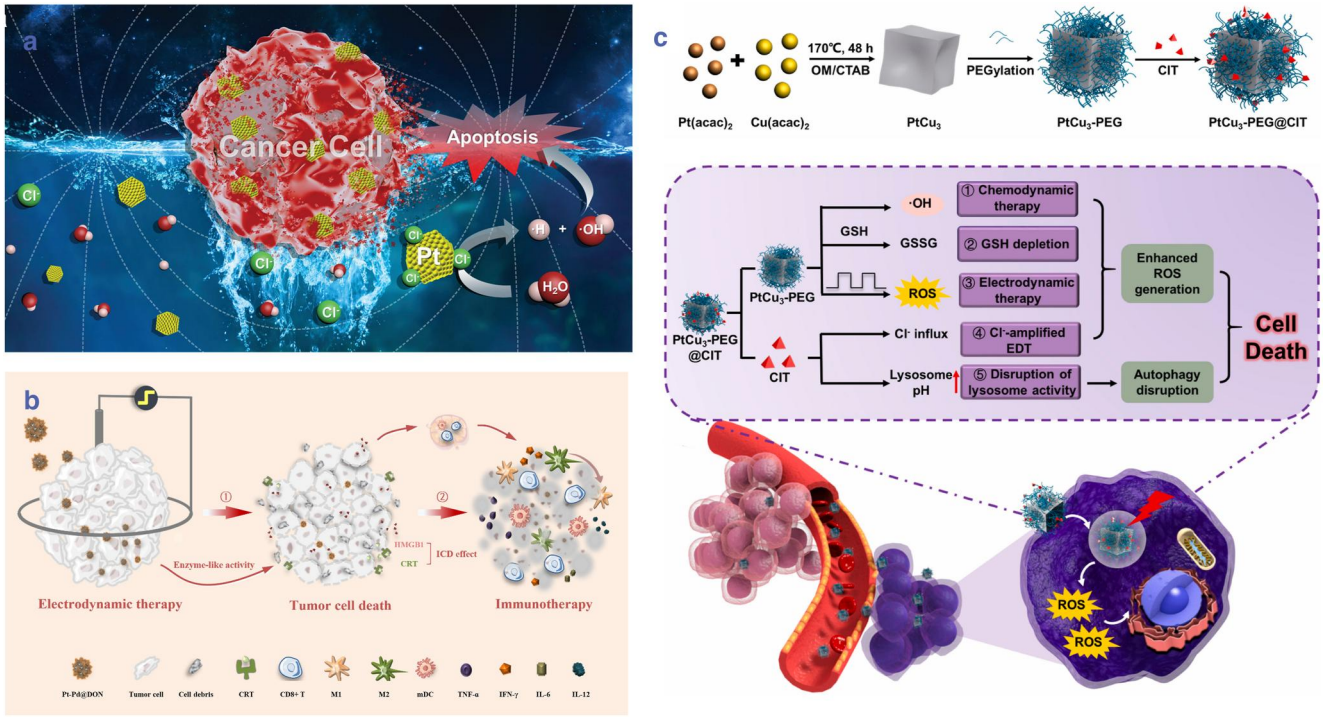

FIGURE 8 (a) Schematic diagram of Pt nanorods for electrodynamic cancer therapy. Reproduced with permission.[116] Copyright 2019, Wiley-VCH. (b) Schematic diagram of electrodynamic-immunotherapy with Pt–Pd@DON. Reproduced with permission.[117] Copyright 2022, American Chemical Society. (c) The synthetic process and EDT-based combinational therapy of $PtCu_3$-PEG@CIT nanoparticles. Reproduced according to the terms of the CC-BY license.[118]

This therapy coupled EDT with chemodynamical phenomena and glutathione (GSH) depletion.[122] The Fe_3O_4@Pt NPs nanoparticles could effectively induce ROS generation through the catalytic reaction on the surface of Pt nanoparticles under the electric field. And the nanoparticles could catalyze intracellular ROS generation from H_2O_2 through the Fenton reaction at the same time. In addition, Fe^{3+} released from Fe_3O_4@Pt NPs under acidic conditions tumor cells rapidly depleted GSH and inhibited ROS scavenging, thereby enhancing the antitumor efficacy. Since it is difficult to achieve long-term tumor suppression with a single dose of EDT in an immunosuppressive environment, there is a high risk of later tumor recurrence. Yu et al. designed the glutamine antagonist 6-diazo-5-oxo-Lnorleucine (DON)-loaded nanocarrier (Pt-Pd@DON) to reduce the risk of tumor recurrence and metastasis using ROS-mediated ICD effect in combination with tumor immunotherapy[117] (Figure 8b). It has shown promising therapeutic effects in both primary and metastatic tumor models.

The increased concentration of Cl^- is beneficial for ROS production and tumor suppression. Some researchers have enhanced the effect of tumor treatment by increasing the concentration of Cl^- during treatment.[118,123] For example, Li et al. firstly combined Pt/Cu alloy nanoparticles ($PtC(u)_3$NPs) with Cl^- transporters (CIT) for the purpose of synergistic therapy.[118] In this system, $PtCu_3$ NPs could induce oxides, convert endogenous H_2O_2 to •OH, and consume intracellular glutathione (GSH) under an electric field. Moreover, $PtCu_3$-PEG@CIT NPs would transport extracellular Cl^- and increase the intracellular Cl^- concentration to promote the production of ROS. At the same time, intracellular delivery of CIT increased lysosomal pH, leading to the disruption of autophagy and the weakened treatment resistance (Figure 8c).

EDT has several advantages compared with conventional EchT. However, the insertion of electrodes may cause tumor metastasis and harm to normal tissues. In addition, the biological effects and cytotoxicity of Pt-based nanomaterials in EDT are not well studied. The safe dose range needs to be considered. Some novel non-Pt-based nanomaterials[124] can also be explored and developed for use in EDT.

6 | CONCLUSION AND PERSPECTIVE

The potential of ES in cancer therapy has attracted widespread attention. To advance its clinical application, it is crucial to comprehend the mechanisms underlying the effects of ES on tumor cells and their associated microenvironment. Herein, we systematically explored

the effects of ES on cancer cells. ES produces different effects on cells, depending on the specific parameters of the electrical signals used. By affecting cell membrane proteins, ion channels, cytoskeleton components, and various organelles, ES has been shown to interfere with tumor cell growth, regulate the TIME, and ultimately contribute to tumor treatment. Through this mechanism, ES points a promising direction toward the ultimate goal of curing cancer.

From a mechanistic point of view, despite evidence suggesting that ES can enhance the efficacy of radiotherapy (RT) and chemotherapy (CT),[125] the direct-acting targets, precise mechanisms and specific effects of ES remain unclear. Therefore, further genomic and metabolomic tests, such as single-cell RNA sequencing (scRNA-seq) and cytokine monitoring, are necessary to reveal the mechanisms and potential targets of ES treatment.

From a therapeutic standpoint, TTFields have been extensively used in clinics to treat cancer, but so far, they have only been shown to be effective for a small number of astrocytic and neurological tumors. Moreover, TTFields therapy devices are expensive and the technology is monopolized; therefore, it is essential to find alternatives to reduce the associated costs and increase TTFields efficiency, to broaden their use in treating other cancer types. Pulsed ES requires high voltage to induce perforation of tumor cell membranes, and the use of conventional commercial power supplies can trigger unavoidable safety risks during the treatment process. This process is to a certain extent uncontrollable; in addition to eliminating tumors, it causes irreversible damage to other surrounding healthy cells. Therefore, if the target action of the different types of ES in tumors can be clearly revealed, this will be a guiding light to use ES in tumors treatment (Figure 9).

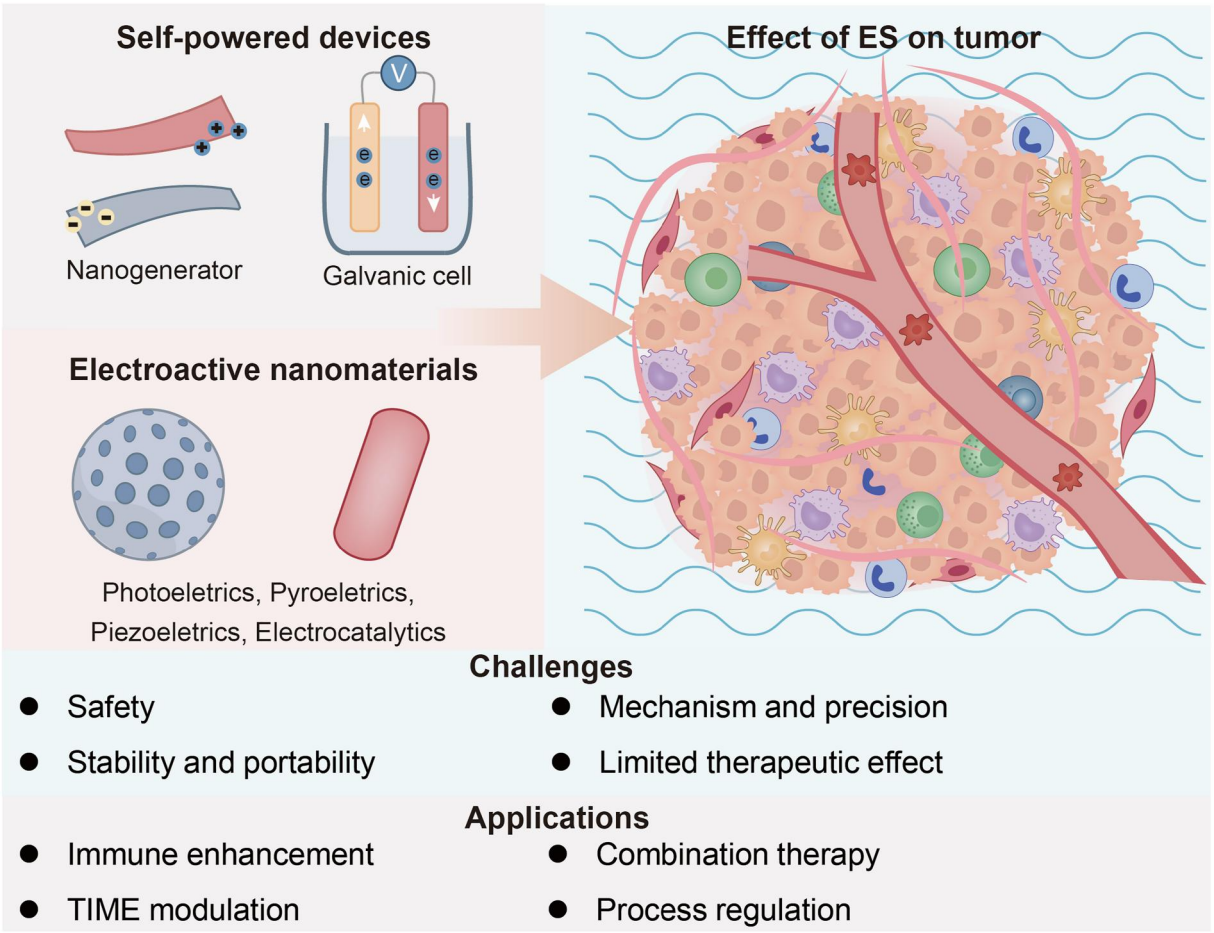

FIGURE 9 The current challenges and potential developments of the ES in cancer treatment. ES for cancer therapy faces the problems of inadequate clinical safety, due to the lack of adequate safety evaluative trials, and the inability of current ES devices to achieve portability and stable output over long periods of time. Additionally, there is a lack of clear mechanisms and the therapeutic effects are limited. Thankfully, ES has the potential for immune enhancement, TIME modulation, and process regulation and has excellent effects when combined with CT, RT, and other therapeutical approaches in treating tumors.[125] CT, chemotherapy; ES, electrical stimulation; RT, radiotherapy; TIME, tumor immune microenvironment.

From a device perspective, despite the availability of more mature and advanced devices, traditional ES modalities such as TTFields remain expensive and inconvenient. Moreover, high-intensity pulsed ES devices require a huge supply of equipment and raise safety concerns, such as tissue damage, muscle irritation and other adverse reactions. In addition, traditional commercial ES devices usually require specially trained medical personnel to operate, which limits the treatment's portability being uncomfortable for patients. What's more, disposing of outdated equipment is a burden on the environment. Therefore, there is a pressing need to develop novel ES devices for effective tumor treatment in virtue of nanomaterials and NG, which offer benefits such as lightweight construction, biosafety, and a wide range of controllability. This constitutes a major challenge that needs to be addressed.

The emergence of nanomaterials and technologies has enriched cancer treatment options and overcome some of the limitations of traditional methods. Compared with some clinical power supplies, nanogenerators offer advantages such as small size, light weight, portability, self-powering, inexpensiveness, high voltage, and low current. However, improving the output stability of the generator is necessary due to the wear resistance of the material. The output of generators is also greatly affected by environmental factors, necessitating the reasonable design of implantable power sources. Currently, the galvanic cells used in tumor therapy mainly take advantages of the products of the reaction process (such as therapeutic gases and free radicals) to achieve the purpose of tumor therapy. And there is not a lot of research in this area. As a macroscopic device, galvanic cell may produce a high electrical output, which should have a certain effect in the tumor treatment through ES.

Nanomaterials with rational design can trigger specific tumor-killing effects through the weak electrical signal under the external stimulation. To a certain extent, nanomaterial delivery can achieve the purpose of targeted therapy. Besides, it causes less trauma to the body compared with traditional ES. Its spatiotemporal controllability can be achieved by external stimuli. However, the main problem faced by electrically dependent stimulus responsive nanomaterials is the efficiency of electron-hole separation. Effectively improving the efficiency of electron-hole separation in materials will greatly promote the tumor treatment effect of materials. At present, methods to promote electron-hole separation in materials mainly include forming heterojunctions on the surface of materials or adjusting oxygen vacancy defects through physical and chemical methods. Reasonable design of the composition and structure of nanomaterials can improve the efficiency of electron-hole separation in materials. Biosafety and biocompatibility are also important factors to be considered. At present, the research of nanomaterials is mostly carried out in animal experiments. Due to the significant individual differences between humans and animals, there is still a certain distance from clinical translation. The delivery efficiency of nanomaterials also has influence on their therapeutic efficacy to some extent. The delivery of nanomaterials is often affected by various physiological environments in the organism, such as biological barriers and first-pass effects, which can be enhanced by biomimetic engineering or modification with biocompatible polymers. A full understanding of the antitumor mechanism of ES and the emerging materials and technologies used in the treatment of ES will enrich the methods of ES for tumor therapy.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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REFERENCES

1. Q. Wu, H. Zhang, H. Liu, *BMEMat* **2023**, *1*, e12010.
2. B. Markelc, G. Sersa, M. Cemazar, *PLoS One* **2013**, *8*, 11.
3. C. Bertacchini, P. M. Margotti, E. Bergamini, A. Lodi, M. Ronchetti, R. Cadossi, *Technol. Cancer Res. Treat.* **2007**, *6*, 313.
4. A. Rossi, O. N. Pakhomova, P. A. Mollica, M. Casciola, U. Mangalanathan, A. G. Pakhomov, C. J. C. Muratori, *Cancers* **2019**, *11*, 2034.
5. E. D. Kirson, Z. Gurvich, R. Schneiderman, E. Dekel, A. Itzhaki, Y. Wasserman, R. Schatzberger, Y. Palti, *Cancer Res.* **2004**, *64*, 3288.
6. J. J. Chamberlain, *Ann. Intern. Med.* **2016**, *315*, 2348.
7. N. Alinezhadbalalami, P. M. Graybill, K. M. Imran, S. S. Verbridge, I. C. Allen, R. V. Davalos, *Bioelectrochemistry* **2021**, *142*, 107886.
8. J. C. Ullery, M. Tarango, C. C. Roth, B. L. J. B. Ibey, *BBRC* **2015**, *458*, 411.
9. S. Mittal, N. V. Klinger, S. K. Michelhaugh, G. R. Barger, S. C. Pannullo, C. J. J. o. n. Juhász, *J. Neurosurg.* **2017**, *128*, 414.

10. M. Giladi, M. Munster, R. S. Schneiderman, T. Voloshin, Y. Porat, R. Blat, K. Zielinska-Chomej, P. Hååg, Z. e. Bomzon, E. D. J. R. O. Kirson, *Radiat. Oncol.* **2017**, *12*, 1.
11. H. Bai, J. V. Forrester, M. J. C. Zhao, *Cytokine* **2011**, *55*, 110.
12. K. Geng, J. Wang, P. Liu, X. Tian, H. Liu, X. Wang, C. Hu, H. Yan, *Am. J. Physiol.: Cell Phsiol.* **2019**, *317*, C277.
13. E. Wang, Y. Yin, M. Zhao, J. V. Forrester, C. D. McCaig, *FASEB J.* **2003**, *17*, 1.
14. Y. Kong, F. Liu, B. Ma, J. Duan, W. Yuan, Y. Sang, L. Han, S. Wang, H. J. A. S. Liu, *Adv. Sci.* **2021**, *8*, 2100962.
15. F. Hilpert, A. Heiser, W. Wieckhorst, N. Arnold, D. Kabelitz, W. Jonat, J. Pfisterer, *Scand. J Immunol.* **2005**, *62*, 399.
16. I. Goswami, J. B. Perry, M. E. Allen, D. A. Brown, M. R. von Spakovsky, S. S. Verbridge, *Biophys. J.* **2018**, *114*, 2951.
17. B. J. Burbach, S. D. O'Flanagan, Q. Shao, K. M. Young, J. R. Slaughter, M. R. Rollins, T. J. L. Street, V. E. Granger, L. K. Beura, S. M. Azarin, S. Ramadhyani, B. R. Forsyth, J. C. Bischof, Y. Shimizu, *Nat. Commun.* **2021**, *12*, 3862.
18. L. Carr, M. Golzio, R. Orlacchio, G. Alberola, J. Kolosnjaj-Tabi, P. Leveque, D. Arnaud-Cormos, M.-P Rols, *Bioelectrochemistry* **2021**, *141*, 107839.
19. S. J. Beebe, P. Fox, L. Rec, K. Somers, R. H. Stark, K. H. Schoenbach, *IEEE Trans. Plasma Sci. IEEE Nucl. Plasma Sci. Soc.* **2002**, *30*, 286.
20. J. A. Tuszynski, C. Wenger, D. E. Friesen, J. Preto, *Int. J. Environ. Res. Public Health* **2016**, *13*, 1128.
21. C. Wenger, P. C. Miranda, R. Salvador, A. Thielscher, Z. Bomzon, M. Giladi, M. M. Mrugala, A. R. Korshoej, *IEEE Rev. Biomed. Eng.* **2018**, *11*, 195.
22. Y. Porat, M. Giladi, R. S. Schneiderman, R. Blat, A. Shteingauz, E. Zeevi, M. Munster, T. Voloshin, N. Kaynan, *J. Visualized Exp.* **2017**, *123*, e55820.
23. G. Tanzhu, L. Chen, G. Xiao, W. Shi, H. Peng, D. Chen, R. Zhou, *Cell Death Dis.* **2022**, *8*, 416.
24. S. Shams, C. B. Patel, *J. Mol. Cell. Biol.* **2022**, *14*, mjac047.
25. L. Berkelmann, A. Bader, S. Meshksar, A. Dierks, G. Hatipoglu Majernik, J. K. Krauss, K. Schwabe, D. Manteuffel, A. Ngezahayo, *Sci. Rep.* **2019**, *9*, 7362.
26. H. T. Le, M. Staelens, D. Lazzari, G. Chan, J. A. Tuszyński, *Cells* **2022**, *11*, 2712.
27. M. Giladi, K. Zielinska-Chomej, A. Tichon, J. Tu, R. S. Schneiderman, K. Viktorsson, E. D. Kirson, Y. Palti, R. M. Lewensohn, *ASCO* **2014**, *32*, e22239.
28. M. Giladi, M. Munster, R. Schneiderman, T. Voloshin, Y. Porat, R. Blat, S. Sherbo, Z. Bomzon, E. Kirson, U. Weinberg, Y. Palti, *Biol. Phys.* **2015**, *93*, E524.
29. Y.-J. Lee, H. W. Seo, J.-H. Baek, S. H. Lim, S.-G. Hwang, E. H. Kim, *Sci. Rep.* **2020**, *10*, 12272.
30. M. Wang, C. Zhang, X. Wang, H. Yu, H. Zhang, J. Xu, J. Zhao, X. Jiang, *Mol. Cell* **2021**, *11*, 1069.
31. H. Hanna, A. Denzi, M. Liberti, F. M. André, L. M. Mir, *Sci. Rep.* **2017**, *7*, 1.
32. V. Nesin, A. G. Pakhomov, *Bioelectromagnetics* **2012**, *33*, 443.
33. A. Puiggalí-Jou, L. J. Del Valle, C. J. M. Alemán, *Materials* **2019**, *12*, 2633.
34. R. Mukherjee, W. T. Rivers, J. M. Ruddy, R. G. Matthews, C. N. Koval, R. A. Plyler, E. I. Chang, R. K. Patel, C. B. Kern, R. E. Stroud, F. G. Spinale, *Circulation* **2010**, *122*, 20.
35. A. Steuer, C. M. Wolff, T. von Woedtke, K.-D. Weltmann, J. F. Kolb, *PLoS One* **2018**, *13*, e0204916.
36. P. Hong, N. Kudulaiti, S. Wu, J. Nie, D. Zhuang, *Expert Rev. Mol. Diagn.* **2022**, *22*, 19.
37. E. Bahar, H. Kim, H. Yoon, *Int. J. Mol. Sci.* **2016**, *17*, 1558.
38. W.-J. Chen, Z.-A. Xiong, M. Zhang, C.-G. Yao, Z.-Y. Zhao, Y.-Y. Hua, W. Zhou, *Int. J. Oncol.* **2013**, *42*, 963.
39. Y. Hamada, Y. Furumoto, A. Izutani, S. Taniuchi, M. Miyake, M. Oyadomari, K. Teranishi, N. Shimomura, S. Oyadomari, *PLoS One* **2020**, *15*, e0229948.
40. J. Zhuang, W. Ren, Y. Jing, J. F. Kolb, *IEEE Trans. Dielectr. Electr. Insul.* **2012**, *19*, 609.
41. G. Qi, B. Wang, Y. Zhang, H. Li, C. Li, W. Xu, Y. Jin, *Anal. Chem.* **2019**, *91*, 9571.
42. Y.-Y. Hua, X.-S. Wang, Y. Zhang, C.-G. Yao, X.-M. Zhang, Z.-A. Xiong, *Mol. Med. Rep.* **2012**, *5*, 981.
43. H. Yoshida, *FEBS J.* **2007**, *274*, 630.
44. R. Sano, J. C. Reed, *Mol. Cell. Rep.* **2013**, *1833*, 3460.
45. A. S. Lee, L. M. J. C. b. Hendershot, *Therapy* **2006**, *5*, 721.
46. H. Fukuda, M. Miyake, H. Hirai, K. Teranishi, N. Shimomura, S. Oyadomari, *EEE PPC* **2015**, p. 1.
47. D. T. Rutkowski, J. Wu, S.-H. Back, M. U. Callaghan, S. P. Ferris, J. Iqbal, R. Clark, H. Miao, J. R. Hassler, J. Fornek, M. G. Katze, M. M. Hussain, B. Song, J. Swathirajan, J. Wang, G. D. Y. Yau, R. J. Kaufman, *Dev. Cell* **2008**, *15*, 829.
48. S. J. Beebe, R. Joshi, K. H. Schoenbach, S. Xiao, *Ultrashort Electric Pulse Effects in Biology and Medicine* **2021**, 127.
49. M. Corazzari, M. Gagliardi, G. M. Fimia, M. Piacentini, *Front. Oncol.* **2017**, *7*, 78.
50. K. Morotomi-Yano, S. Oyadomari, H. Akiyama, K. Yano, *Exp. Cell. Res.* **2012**, *318*, 1733.
51. P. T. Vernier, Y. Sun, L. Marcu, S. Salemi, C. M. Craft, M. A. Gundersen, *Biochem. Biophys. Res. Commun.* **2003**, *310*, 286.
52. I. Semenov, S. Xiao, A. G. Pakhomov, *Biochim. Biophys. Acta, Biomembr.* **2013**, *1828*, 981.
53. M. Rols, F. Dahhou, K. Mishra, J. Teissié, *Biochemistry* **1990**, *29*, 2960.
54. Y. Porat, A. Shteingauz, M. Giladi, R. S. Schneiderman, T. Voloshin, M. Munster, R. Blat, E. D. Kirson, U. Weinberg, Y. Palti, *Cancer Res.* **2016**, *76*, 3543.
55. S. J. Beebe, B. P. Lassiter, S. Guo, *Cancers* **2018**, *10*, 97.
56. A. Shteingauz, Y. Porat, M. Giladi, R. Schneiderman, T. Voloshin, M. Munster, E. Kirson, U. Weinberg, Y. Palti, *Cancer Res.* **2018**, *78*, 1343.
57. A. Shteingauz, Y. Porat, T. Voloshin, R. S. Schneiderman, M. Munster, E. Zeevi, N. Kaynan, K. Gotlib, M. Giladi, E. D. Kirson, U. Weinberg, A. Kinzel, Y. Palti, *Cell Death Dis.* **2018**, *9*, 1074.
58. N. Mizushima, *Genes Dev.* **2007**, *21*, 2861.
59. M. Binnewies, E. W. Roberts, K. Kersten, V. Chan, D. F. Fearon, M. Merad, L. M. Coussens, D. I. Gabrilovich, S. Ostrand-Rosenberg, C. C. Hedrick, R. H. Vonderheide, M. J. Pittet, R. K. Jain, W. Zou, T. K. Howcroft, E. C. Woodhouse, R. A. Weinberg, M. F. Krummel, *Nat. Med.* **2018**, *24*, 541.
60. T. Voloshin, S. Davidi, N. Kaynan, R. Schneiderman, A. Volodin, M. Giladi, U. Weinberg, Y. Palti, *Cancer Res.* **2020**, *80*, 6662.

61. C. Li, C. Xiao, L. Zhan, Z. Zhang, J. Xing, J. Zhai, Z. Zhou, G. Tan, J. Piao, Y. Zhou, S. Qi, Z. Wang, P. Yu, C. Ning, *Bioact. Mater.* **2022**, *18*, 399.
62. M. Bustamante, R. Fernández-Verdejo, E. Jaimovich, S. Buvinic, *Am. J. Physiol.: Endocrinol. Metab.* **2014**, *306*, E869.
63. M. Zhao, H. Bai, E. Wang, J. V. Forrester, C. D. McCaig, *J. Cell Sci.* **2004**, *117*, 397.
64. S. L. Amaral, J. R. Linderman, M. M. Morse, A. S. Greene, *Microcirculation* **2001**, *8*, 57.
65. S. G. Gürgen, O. Sayın, F. Çetin, A. Tuç Yücel, *Inflammation* **2014**, *37*, 775.
66. X. Wei, L. Guan, P. Fan, X. Liu, R. Liu, Y. Liu, H. Bai, *J. Vasc. Res.* **2020**, *57*, 195.
67. O. Yarishkin, J. M. Baumann, D. Križaj, *Channels* **2019**, *13*, 168.
68. S. Nam, V. K. Gupta, H.-p. Lee, J. Y. Lee, K. M. Wisdom, S. Varma, E. M. Flaum, C. Davis, R. B. West, O. Chaudhuri, *Sci. Adv.* **2019**, *5*, eaaw6171.
69. R. Seger, E. G. Krebs, *Faseb J.* **1995**, *9*, 726.
70. K. Morotomi-Yano, H. Akiyama, K.-i. Yano, *Arch. Biochem. Biophys.* **2011**, *515*, 99.
71. A. Q. Sheikh, T. Taghian, B. Hemingway, H. Cho, A. B. Kogan, D. A. Narmoneva, *J. R. Soc., Interface* **2013**, *10*, 20120548.
72. J.-I. Park, K.-H. Song, S.-Y. Jung, J. Ahn, S.-G. Hwang, J. Kim, E. H. Kim, J.-Y. Song, *Technol. Cancer Res. Treat.* **2019**, *18*, 1533033819868225.
73. M. Mattson, M. Meffert, *Cell Death Differ.* **2006**, *13*, 852.
74. Z. Ren, X. Chen, G. Cui, S. Yin, L. Chen, J. Jiang, Z. Hu, H. Xie, S. Zheng, L. Zhou, *PLoS One* **2013**, *8*, e74322.
75. C. Henríquez-Olguín, F. Altamirano, D. Valladares, J. R. López, P. D. Allen, E. Jaimovich, *Biochim. Biophys. Acta, Gen. Subj.* **2015**, *1852*, 1410.
76. J. Kavaliauskaitė, A. Kazlauskaitė, J. R. Lazutka, G. Mozolevskis, A. Stirkė, *Int. J. Mol. Sci.* **2021**, *23*, 451.
77. Z. L. Wang, J. Song, *Science* **2006**, *312*, 242.
78. F.-R. Fan, Z.-Q. Tian, Z. L. Wang, *Nano Energy* **2012**, *1*, 328.
79. Y. Cao, Y. Yang, X. Qu, B. Shi, L. Xu, J. Xue, C. Wang, Y. Bai, Y. Gai, D. Luo, Z. Li, *Small Methods* **2022**, *6*, 2101529.
80. Y. Gai, E. Wang, M. Liu, L. Xie, Y. Bai, Y. Yang, J. Xue, X. Qu, Y. Xi, L. Li, D. Luo, Z. Li, *Small Methods* **2022**, *6*, 2200653.
81. J. Cao, X. Fu, H. Zhu, Z. Qu, Y. Qi, Z. Zhang, Z. Zhang, G. Cheng, C. Zhang, J. Ding, *Small Methods* **2022**, *6*, 2200588.
82. C. Zhao, H. Feng, L. Zhang, Z. Li, Y. Zou, P. Tan, H. Ouyang, D. Jiang, M. Yu, C. Wang, H. Li, L. Xu, W. Wei, Z. Li, *Adv. Funct. Mater.* **2019**, *29*, 1808640.
83. C. Zhao, Q. Shi, H. Li, X. Cui, Y. Xi, Y. Cao, Z. Xiang, F. Li, J. Sun, J. Liu, T. Li, W. Wei, B. Xiong, Z. Li, *ACS Nano* **2022**, *16*, 8493.
84. C. Zhao, Y. Yang, X. Cui, Y. Shan, J. Xue, D. Jiang, J. Sun, N. Li, Z. Li, A. Yang, *Materials* **2022**, *15*, 2060.
85. S. Yao, M. Zheng, Z. Wang, Y. Zhao, S. Wang, Z. Liu, Z. Li, Y. Guan, Z. L. Wang, L. Li, *Adv. Mater.* **2022**, *34*, 2205881.
86. Y. Yang, X. Hu, Y. Liu, B. Ouyang, J. Zhang, H. Jin, Z. Yu, R. Liu, Z. Li, L. Jiang, X. Lin, B. Xu, *Sci. Adv.* **2022**, *8*, eabm5023.
87. Z. Liu, L. Xu, Q. Zheng, Y. Kang, B. Shi, D. Jiang, H. Li, X. Qu, Y. Fan, Z. L. Wang, Z. Li, *ACS Nano* **2020**, *14*, 8074.
88. B. Chu, X. Qin, Q. Zhu, H. Wang, Z. Wen, X. Sun, Y. He, S.-T. Lee, *Nano Energy* **2022**, *100*, 107471.
89. N. Yang, F. Gong, B. Liu, Y. Hao, Y. Chao, H. Lei, X. Yang, Y. Gong, X. Wang, Z. Liu, L. Cheng, *Nat. Commun.* **2022**, *13*, 2336.
90. J. Huang, P. Yu, M. Liao, X. Dong, J. Xu, J. Ming, D. Bin, Y. Wang, F. Zhang, Y. Xia, *Sci. Adv.* **2023**, *9*, eadf3992.
91. Q. Y. Zheng, X. M. Liu, Y. F. Zheng, K. W. K. Yeung, Z. D. Cui, Y. Q. Liang, Z. Y. Li, S. L. Zhu, X. B. Wang, S. L. Wu, *Chem. Soc. Rev.* **2021**, *50*, 5086.
92. C. Y. Wang, N. Tian, T. Y. Ma, Y. H. Zhang, H. W. Huang, *Nano Energy* **2020**, *78*, 105371.
93. A. Cafarelli, A. Marino, L. Vannozzi, J. Puigmarti-Luis, S. Pane, G. Ciofani, L. Ricotti, *ACS Nano* **2021**, *15*, 11066.
94. Y. L. Wan, L. H. Fu, C. Y. Li, J. Lin, P. Huang, *Adv. Mater.* **2021**, *33*, 2103978.
95. S. L. Gai, G. X. Yang, P. P. Yang, F. He, J. Lin, D. Y. Jin, B. G. Xing, *Nano Today* **2018**, *19*, 146.
96. J. C. Li, S. Q. Wang, F. Fontana, C. Tapeinos, M. A. Shahbazi, H. J. Han, H. A. Santos, *Bioact. Mater.* **2023**, *23*, 471.
97. M. H. Lan, S. J. Zhao, W. M. Liu, C. S. Lee, W. J. Zhang, P. F. Wang, *Adv. Healthcare Mater.* **2019**, *8*, 1900132.
98. R. C. Gilson, K. C. L. Black, D. D. Lane, S. Achilefu, *Angew. Chem., Int. Ed.* **2017**, *56*, 10717.
99. N. Kotagiri, G. P. Sudlow, W. J. Akers, S. Achilefu, *Nat. Nanotechnol.* **2015**, *10*, 370.
100. Z. Zhang, M. K. G. Jayakumar, X. Zheng, S. Shikha, Y. Zhang, A. Bansal, D. J. J. Poon, P. L. Chu, E. L. L. Yeo, M. L. K. Chua, S. K. Chee, Y. Zhang, *Nat. Commun.* **2019**, *10*, 4586.
101. S. S. Lucky, N. Muhammad Idris, Z. Li, K. Huang, K. C. Soo, Y. Zhang, *ACS Nano* **2015**, *9*, 191.
102. X.-N. Wang, M.-T. Niu, J.-X. Fan, Q.-W. Chen, X.-Z. Zhang, *Nano Lett.* **2021**, *21*, 4270.
103. D. Yang, G. Yang, Q. Sun, S. Gai, F. He, Y. Dai, C. Zhong, P. Yang, *Adv. Healthcare Mater.* **2018**, *7*, 1800042.
104. Z. Tang, P. Zhao, D. Ni, Y. Liu, M. Zhang, H. Wang, H. Zhang, H. Gao, Z. Yao, W. Bu, *Mater. Horiz.* **2018**, *5*, 946.
105. Y. Wang, X. Dai, C. Dong, W. Guo, Z. Xu, Y. Chen, H. Xiang, R. Zhang, *Adv. Mater.* **2022**, *34*, 2106773.
106. Y. Chang, Y. Cheng, R. Zheng, X. Wu, P. Song, Y. Wang, J. Yan, H. Zhang, *Nano Today* **2021**, *38*, 101110.
107. Y. He, Z. Li, C. Cong, F. Ye, J. Yang, X. Zhang, Y. Yuan, Z. Ma, K. Zhang, Y. Lin, L. Zheng, X.-J. Liang, D. Gao, *ACS Nano* **2021**, *15*, 10488.
108. Y. Zhao, S. Wang, Y. Ding, Z. Zhang, T. Huang, Y. Zhang, X. Wan, Z. L. Wang, L. Li, *ACS Nano* **2022**, *16*, 9304.
109. Z. Li, T. Zhang, F. Fan, F. Gao, H. Ji, L. Yang, *J. Phys. Chem. Lett.* **2020**, *11*, 1228.
110. P. Zhu, Y. Chen, J. Shi, *Adv. Mater.* **2020**, *32*, 2001976.
111. C. Li, C. Xiao, L. Zhan, Z. Zhang, J. Xing, J. Zhai, Z. Zhou, G. Tan, J. Piao, Y. Zhou, S. Qi, Z. Wang, P. Yu, C. Ning, *Bioact. Mater.* **2022**, *18*, 399.
112. K. Ma, G. Qi, B. Wang, T. Yu, Y. Zhang, H. Li, S. A. Kitte, Y. Jin, *Nano Energy* **2021**, *87*, 106208.
113. S. Chen, P. Zhu, L. Mao, W. Wu, H. Lin, D. Xu, X. Lu, J. Shi, *Adv. Mater.* **2023**, *12*, 2208256.
114. H. Fukui, R. W.-Y. Chow, J. Xie, Y. Y. Foo, C. H. Yap, N. Minc, N. Mochizuki, J. Vermot, *Science* **2021**, *374*, 351.
115. X. Y. Sun, B. Yuan, W. Rao, J. Liu, *Biomaterials* **2017**, *146*, 156.

116. T. X. Gu, Y. Wang, Y. H. Lu, L. Cheng, L. Z. Feng, H. Zhang, X. Li, G. R. Han, Z. Liu, *Adv. Mater.* **2019**, *31*, 1806803.
117. G. Chen, Q. Xu, Z. Z. Feng, Q. Q. Xu, X. H. Zhang, Y. Y. Yang, Y. X. Zhang, X. J. Liang, Z. Q. Yu, M. Yu, *ACS Nano* **2022**, *16*, 951.
118. T. Chen, G. R. Han, X. Li, *Bioact. Mater.* **2022**, *12*, 143.
119. T. Chen, T. X. Gu, L. Cheng, X. Li, G. R. Han, Z. Liu, *Biomaterials* **2020**, *255*, 120202.
120. T. X. Gu, T. Chen, L. Cheng, X. Li, G. R. Han, Z. Liu, *Nano Res.* **2020**, *13*, 2209.
121. Z. J. Lu, J. Y. Gao, C. Fang, Y. Zhou, X. Li, G. R. Han, *Adv. Sci.* **2020**, *7*, 2001223.
122. T. Chen, Q. Chu, M. Y. Li, G. R. Han, X. Li, *J. Nanobiotechnology* **2021**, *19*, 206.
123. T. Chen, Y. K. Fu, R. Y. Zhang, G. R. Han, X. Li, *Biomater. Sci.* **2022**, *10*, 376.
124. Y. Song, Y. Sun, M. L. Tang, Z. Y. Yue, J. T. Ni, J. G. Zhao, W. X. Wang, T. D. Sun, L. X. Shi, L. Wang, *ACS Appl. Mater. Interface* **2022**, *14*, 4914.
125. G. Peng, K. Masood, O. Gantz, U. Sinha, *J. Surg. Oncol.* **2016**, *114*, 27.

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