Review Article

Application of Piezoelectric Catalytic Materials in Tumor Therapy

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Cancer is a major global health issue, the 3rd most common and 2nd deadliest among cancers. Its progression usually includes the stage from polyp formation to adenocarcinoma, influenced by factors such as age, genetic susceptibility, and environmental conditions such as diet and lifestyle. Typical therapy approaches encompass chemotherapy, surgery and radiation, with chemotherapy being crucial for disease recurrence and spread due to associated risks. Recent advancements in treatments include molecular-targeted and immunotherapy, but challenges such as drug resistance and low response rates continue to exist. Latest research has illuminated how dietary habits and gut microorganisms impact colorectal cancer treatment, revealing that the makeup of gut microbiota is key to the effectiveness of chemotherapy and immunotherapy treatments. The piezoelectric effect, especially the mechanical stress induced by ultrasonic waves shows considerable potential in generating reactive oxygen species for treating cancer.

Key words: Tumor therapy, chemotherapy, drug resistance, piezoelectric, polyps

CURRENT STATUS OF COLORECTAL CANCER (CRC)

Around the world, CRC often found, occupies the 3rd spot and ranks as the 2nd most lethal, posing a considerable risk to health and safety in the community[1]. The progression of CRC typically occurs in several stages, beginning with the formation of polyps and advancing to adenocarcinoma, which often turns more aggressive. Chemical agents for CRC, including platinum, 5-Fluorouracil (5-FU), irinotecan and similar substances, are commonly used in treatment. Therapies focused on specific molecules and immunotherapies have surfaced as crucial divergent treatments for CRC. Their effectiveness hinges on precise identification of various subtypes and recognizing genetic irregularities or heightened tumor-promoting proteins activation. Addressing the emerging resistance in kinase-targeted treatments and controlling the sluggish reaction rates to immune therapies poses significant challenges. Latest studies underscore the critical need to change food patterns and gut microbiota to manage CRC. Apart from its role in digestion and immune response, the colon serves as a sanctuary for diverse microorganisms present in the gut microbiota. The pivotal function of metabolic activities and signaling entities in the interplay between microbiota and the host is to maintain intestinal balance. Research indicates that gut microbiota plays a role in determining the efficacy and adverse effects of chemotherapy and immunotherapy for cancer[2]. Individuals suffering from CRC and similar cancer types commonly show variations in their intestinal microbial makeup, a phenomenon termed dysbiosis[3]. The alteration of gut microbiota *via* fecal transplants and dietary modifications appears to hold potential for therapeutic uses in diverse cancer types, whether used independently or in combination with other therapies.

Core principles of piezoelectric processes and the development of piezoelectric substances:

There are two proposed mechanisms; the piezoelectric catalytic effect and the piezoelectric photonic effect. The piezoelectric catalytic effect denotes the mechanical pressure ultrasound exerts on semiconductor substances, fostering their interaction and environmental factors, leading to the generation of Reactive Oxygen Species (ROS). The piezoelectric photon phenomenon implies that ultrasound photons

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interact with the semiconductor substance to generate ROS[4].

Piezoelectric catalytic effect:

Known as the piezocatalytic effect (first termed piezochemical effect by Hong *et al.*); the process primarily employs ultrasonic stimulation for facilitating direct water breakdown. Polarization serves as a pivotal factor in the segregation of carriers. Exposure to ultrasonic waves causes bubble bursting to generate pressure, leading to changes in the piezoelectric semiconductor's shape and modifications in its surface charges. When these molecules of hydrogen combine with water molecules, it leads to the formation of hydrogen gas and hydroxyl radicals. Electron are generated by groups of negatively charged hydroxyls[5]. Piezoelectric semiconductors generate free radicals, which subsequently interact with the oxygen molecules in their environment. Such reactions lead to the formation of peroxide derivatives and alcohol-oxidized substances. Certain chemical reactions contribute to the peroxidation of membrane lipids, rendering them unstable and exposing cells more susceptible to harm due to shear and ultrasonic pressure[5]. Polarization charges in semiconductor heterojunctions are crucial in controlling band bending and charge transfer, offering an innovative approach to manage the dynamic behavior of charge carriers efficiently[6].

Piezoelectric photon effect:

Wang *et al*.[7] pioneered the innovative piezophoton effect, merging piezoelectric properties, photoexcitation and the features of semiconductors. This occurrence profoundly affects the movement of excited carriers inside semiconductors, thereby modifying their catalytic characteristics. Precise adjustment of the band configuration is facilitated through the piezoelectrically polarized charge located at the intersection of various structures, along with the transition of carriers caused by light. When a bubble reaches its maximum contraction point due to cavitation. Upon the heat and pressure within a gas bubble, the gas transforms into plasma, marked by a transient but intense light emission, termed acoustic luminescence. The energy released *via* photons during this process is sufficient to activate electrons inside piezoelectric semiconductors. Under certain circumstances, electrons shift from the valence to the conduction bands, leading to the creation of electron-hole pairs that subsequently move to different regions of the piezoelectric semiconductor surface. If the potential of the semiconductor's conduction band falls beneath the redox potential of O_2/O_2- (-0.33 V), it facilitates the transformation of O_2 into O_2-.

When a photo stimulated piezoelectric semiconductor interacts with an electrolyte solution, the photo generated carrier moves through the solid-liquid interface, shifting the semiconductor's energy spectral arrangement. Ultrasound irradiation triggers the piezoelectric effect, leading to the natural creation of an internal electric field from the polarized charge, which is distinct from conventional photocatalytic methods. A band on the surface when a charge is positively polarized, it tends to bend downwards. The surface of the piezoelectric semiconductor exhibits an elevated potential, thereby facilitating electron migration towards the electrolyte solution, which slightly diminishes its reducing power, while impeding pore migration towards the electrolyte solution[8]. Surface bands, bearing negative polarizing charges, angle upward, hindering electron flow towards the electrolyte solution and facilitating the movement of holes. Utilizing the piezophoton effect and selecting piezoelectric semiconductor nanomaterials that obstruct the production of OH- or O_2- in their band formations can improve the catalytic process for generating ROS[9].

APPLICATION OF PIEZOELECTRIC CATALYSIS IN TUMOR THERAPY

Piezoelectric protein:

It is still not clearly understood how collagen the major structural protein of the extracellular matrix of tissues serve in bones' piezoelectricity though triphasic model indicates collagen's influence in this aspect. There is current literature advances that attempt to explain the emergence of the piezoelectric effect in collagen fibrils[10]. Hypotheses of retaining ferroelectric properties include the existence of the non-centrosymmetric structures at molecular level, polar bonds at molecular level, the reorientation of the C=O-NH bonds within the α-helix structure and polarization of the hydrogen bonds in collagen. Testing a recent investigation, it has been seen that piezoelectricity is generated in collagen as a result of the movement of permanent dipoles associated with individual charged polar residues, aligned and vibrating with varying amplitude along the longitudinal axis of the collagen fiber. For bone and tendon derived collagens the shear piezoelectric constants have been reported as d14 which lies within range 0.

M13 phage shows a wide range of applications as a functional material in the fields of energy harvesting, chemical sensing, and tissue regeneration[11]. It is a filamentous bacteriophage 880 nm long and 6.6 nm wide containing single-stranded Deoxyribonucleic Acid (DNA) wrapped by 2700 major proteins (VIII) covered by five minor proteins (III/VI or VIII/IX) at the top or bottom. The major proteins are tilted about 20° relative to the DNA axis and are arranged in a fivefold rotational symmetry and twofold helical symmetry. Each major protein has a dipole moment pointing toward the DNA axis, which permanently polarizes the phage both axially and radially.

Piezoelectric peptide:

Glycine, an amphipathic ionic amino acid, serves as a perfect foundational component for the study of polycrystalline crystallization. Crystalline glycine manifests in three distinct forms; Alpha (α), Beta (β) and Gamma (γ)-structures, where the β and γ-structures demonstrate shear piezoelectricity, attributed to their asymmetrical structure. Similar to inorganic materials, the emergence of piezoelectricity is attributed to the ion displacement inside the crystal, leading to the localized generation of dipoles and the material's general polarization. Amino acids characterized by a β structure demonstrate properties that are shear piezoelectric. Extends to around 190 pm/V d16, similar to the standard piezoelectric constants observed in Barium titanate ($BaTiO_3$).

Comprising two phenylalanine (F) amino acids, peptide-based diphenylalanine (FF) has the capability to autonomously form peptide nanotubes and microcrystals. Observations indicate that these formations can assume diverse forms, execute various functions, and synthetic B exhibits in compatibility and a significant Young's modulus. Numerous research efforts are devoted to understanding the piezoelectric characteristics of nanostructured diphenylalanine, attributable to its asymmetrical hexagonal spatial group. We will highlight how these crystals elucidate physical phenomena like piezoelectricity, generation of second nonlinear harmonics, and optical action. High shear piezoelectric constants for peptide nanotubes have been documented, aligning with the most recent measurements of d15=60 pm/V. Breaking down each layer to enhance the procedure and ensure even distribution of semi-crystalline films, termed a curved moon face driven self-assembly. The method facilitated the creation of diphenylalanine nanotube films with unidirectional polarization, exhibiting d15 values from 45 nm/V to over 100 pm/V in more crystalline formations. The piezoelectricity characteristic of the peptide nanostructures was achieved with the assembly of single microbars in a vertical orientation preferably[12].

Other piezoelectric biopolymers:

Polyvinylidene Fluoride (PVDF) films exhibit one of the highest piezoelectric properties among all piezoelectric polymers discovered so far. PVDF possesses five distinct crystal structures; α, β, γ, Delta (δ), and Epsilon (ε), with the β-phase PVDF exhibiting a normal piezoelectric constant of d33=-33 pC/N. How does the sensitivity of this material provide excellent piezoelectric properties? The branched fluorine atoms increase in size and electronegativity of large Van der Waals radii fluorine. As a result, one gets a polar escape dipole moment in each PVDF unit, which is oriented perpendicular to the polymer chain. These changes take place as the material enters the beta phase where the orthogonal crystal structure orients the fluorine and hydrogen branches parallel to each other therefore increasing the net dipole moment hence the piezoelectric effect. Nonetheless, the positions of the fluorine and hydrogen branches antiparallel means that these vectors actually oppose each other, which leads to the absence of the net dipole moment. Here, the hexagonal structure of the alpha phase is present and dipoles are encompassed. The negative piezoelectric effect is the result of an applied electric field that alters the place of stability of electron molecular orbitals and therefore the charge distribution pattern in the crystal. To augment the piezoelectric constant, copolymer techniques have been employed, involving the incorporation of Trifluoroethylene (TrFE), Hexafluoropropylene (HPF), or Trifluorochloroethylene (CTFE) through conjugation.

Known as Poly L-Lactic Acid (PLLA), this polycrystalline polymer is esteemed for its exceptional biodegradability and compatibility with biological systems. When thermodynamically stable, it develops α-crystal framework where the dipoles formed by the carbonyl group (C=O) remain misaligned with the primary. In response to external factors like electrospinning, these dipoles align unidirectionally in the direction of stretching, resulting in the creation of the β-crystal structure[13].

The resulting shear piezoelectric properties amount to d14=12 pC/N. The β-crystal PLLA, noted for its helical formation, demonstrates remarkable piezoelectric characteristics sans the necessity for a polling sequence, thus expanding its applicability in biocompatible mobile units. The interest in natural polymers is on the rise, credited to their natural compatibility with biological systems, sparking recent research into their possible use as piezoelectric substances for either implantable or wearable applications in the human anatomy. Filaments display piezoelectricity due to various elements such as their height, the crystallinity of β-lamella, and their alignment. The documented piezoelectric constant stands at d14=-1.5 pC/N.

Zinc oxide (ZnO):

ZnO exhibits a unique crystal structure, marked by a tightly packed density of zinc atoms in a hexagonal pattern and oxygen atoms arranged in tetrahedral formations. The piezoelectricity originate from a hexagonal crystal framework without centrosymmetry, marked by tetrahedral coordination. ZnO, known for its wide-band gap semicoreactivity, was first employed in photodynamic treatment because of its valuable attributes like a significant piezoelectric coefficient, economic value, compatibility with biological systems, and a simple production process. With the growing interest in photodynamic therapy, the potential of ZnO in Sonodynamic Therapy (SDT) is gradually gaining recognition. Piezoelectric nanoparticles can change the form of energy and become capable of separation of charge by reception of light, ultrasound, and radiation. These healthy-skin-toning nanomaterials cause redox reactions by interacting with other molecules in the surroundings of the cell thereby producing electron/hole pairs which in return forms ROS[14]. On the other hand, metal oxides are a good class of catalysts that can be used in preparing the catalyst in question. In this regard, exposing it to certain conditions like high temperature or reduction treatment, elementary oxygen within the lattice is expelled, leading to incorporation and formation of oxygen vacancies[15]. In other words, the surface oxygen vacancies that are available on the outer surface of the material can actually help to move the conduction band to a favorable position which would minimize the band gap and hence allowing for the separation of the electron hole pairs. Following the usage of defect engineering scheme, a nano-platform was synthesized by Jiao *et al*.[16] by employing oxygen-deficient Zirconium dioxide (ZrO_2-x). This platform suppressed the rapid reunification of electron (e–)/hole (h+) pairs with the energy band in the presence of applying external ultrasound stimuli. This enhancement was beneficial to increase yield of (ROS) resulting in Immunogenic Cell Death (ICD) and establish concrete systemic anti-tumor immunity. Utilizing ZnO solely as a sonosensitizer results in lower charge separation efficiency, leading to rapid recombination of charge carriers, hindering the commencement of efficacious reactions. To enhance efficiency, it's suggested to incorporate valuable metals like gold, platinum, and iron into ZnO, serving as a photosensitizer, to develop metal/piezoelectric semiconductor heterojunction formations. Scientists, including He *et al*.[17], have altered ZnO nanoparticles using Au particles, each below 3 nm, to explore the fundamental processes behind this amplification. Such improvements highlighted enhanced carrier reactions, thereby exemplifying a successful approach to increase semiconductor efficacy by integrating metals. The significant efficacy of ZnO has garnered keen attention from scientists due to its prospective use in treatable cancer. Wang *et al*.[7] developed an effective system for sound sensitization by merging ZnO and gold nanoparticles with reduced Graphene Oxide (rGO) nanosheets, which are enveloped in polyvinylpyrrolidone. Utilizing the short band gap in the rGO nanosheets, the electron movement from ZnO to gold nanoparticles was simplified, which effectively decreased the recombination of electron-hole pairs. An improved sensitizer process led to a substantial rise in ROS production, culminating in the eradication of several cancer cell varieties, like U373MG, HeLa, and CT26 cells. Through comprehensive assessments including hemolysis tests, blood type analyses, blood biochemical tests, mouse weight monitoring, and organ histological analyses, the material demonstrated low cytotoxicity and commendable biocompatibility[18]. Ultrasound dynamics possess the capability to induce apoptosis and synergize with multiple apoptotic mechanisms, including augmenting cellular iron sag, a pivotal aspect in tumor therapy. In a study by Hu *et al*. a rational design was employed to engineer a ZnO nano-sensitizer (D-ZnO-PEG NPs) co-doped with Iron (Fe) and Manganese (Mn). They were doped with iron and manganese, which catalyzed the Fenton reaction to effectively produce reactive oxygen species, consuming cellular glutathione to inhibit its consumption of activity, thereby inducing various iron allergies and apoptosis, enhancing the efficiency of SDT against tumors, and achieving an inhibition rate of 92.8 % in a tumor mouse model carrying 4T1 cells. In order to assess the biocompatibility and safety of D-ZnO-PEG NPs both *in vitro* and *in vivo*, a series of experiments were conducted, encompassing Cell Counting Kit-8 (CCK-8) assays, monitoring of body weight, blood routine tests, biochemical routine tests, Hematoxylin and Eosin (H&E) staining, and more. This study presents a novel approach of traditional metal doping aimed at enhancing the performance of nanosensitizers for SDT, which holds significant implications for advancing tumor treatment based on SDT[19]. Given the complexity of tumors, pure ZnO alone often fails to achieve satisfactory therapeutic outcomes, thus necessitating its combination with other treatment modalities. Drawing inspiration from semiconductor catalysis and defect chemistry principles, Liu *et al*.[20] engineered a Gadolinium (Gd)-doped ZnO (D-ZnOx:Gd) semiconductor sonosensitizer enriched with defects. The findings demonstrated that the presence of defects facilitated charge transfer and enhanced the separation of e- and h+. Moreover, the defect-rich D-ZnOx:Gd exhibited a strong capability to adsorb oxygen and water molecules, thereby boosting the generation of ROS. Additionally, defective DZnOx:Gd exhibited favorable absorption capabilities within the NIR-II biological window, which allowed for efficient conversion of light into heat when exposed to NIR-II laser irradiation, enhancing tumor cell elimination. The combined treatment strategy utilizing D-ZnOx and photothermal therapy; Gd demonstrated promising passive targeted tumor accumulation and achieved a high tumor killing rate in both 4T1 cells and mouse models. A thorough evaluation comprising blood biochemical analyses, blood routine analyses, and CCK-8 assays validated the excellent biocompatibility of the material and underscored its potential for future clinical applications. Kang *et al*.[9] spearheaded a pioneering study on cancer therapy that capitalized on the use of piezoelectric photocatalysis. They introduced a novel natural amphibolite nanosheet (NSH700 NSs) featuring a composite structure comprising two piezoelectric catalysts (zinc sulfide and ZnO) and one photocatalyst (Zinc ferrite ($ZnFe_2O_4$)) through heterojunction formations. The synergy of 650 nm laser and ultrasound irradiation facilitated the movement of excited electrons and holes from the interior of zinc sulfide to its surface. This mechanism effectively curbed the recombination of electron-hole pairs and encouraged the interaction between neighboring electrons and holes with ZnFe2O4. The formation of a heterojunction comprising ZnS/$ZnFe_2O_4$/ZnO further adjusted the distribution of surface electron-hole pairs, thus fundamentally modifying the oxidation-reduction potential and enabling substantial production of ROS. Laboratory evaluations of NSH700 nanosheets revealed their remarkable effectiveness in eliminating >90 % of Michigan Cancer Foundation-7 (MCF-7) and HeLa cells, also showing notable tumor reduction in mice with MCF-7 tumors. These nanosheets demonstrated remarkable biocompatibility in both lab settings and natural environments. Subsequent to a 30 d monitoring phase, only a slight buildup of nanosheets was observed in the lungs, heart, and kidneys, affirming their advantageous biosafety classification[21].

$BaTiO_3$:

$BaTiO_3$, known for its remarkable catalytic efficiency and enhanced biological compatibility over conventional lead zirconate titanate (PbZr1-$TiXO_3$ or PZT), has become a key piezoelectric semiconductor in the medical sector, specifically in lead-free perovskite structures[22]. The efficacy of piezoelectric catalysis by substances of Perovskite oxide (ABO_3) is intricately linked to their electronic makeup, inherently influenced by each perovskite's own unit composition. Due to its highly malleable crystal structure, this material is a viable option for designing piezoelectric materials[23]. Exposure to external mechanical stress sparks a reaction with surrounding water O_2, resulting in the generation of reactive oxygen species like hydroxyl radicals, superoxide anions, and monoclinic oxygen.

The REDOX reactions of BTO generate reactive oxygen species, inducing protein malfunction, lipid peroxidation, cellular oxidative stress, and DNA impairment, culminating in cell demise, thus exhibiting promising potential in tumor therapy. The effectiveness of piezoelectric materials in acting as catalysts hinges on aspects like their microstructure, overall size, and the quantity of specific surface area in play. Strvuctures of an ultra-thin nature reduce the distance of charge transfer and are characterized by numerous dangling bonds on the surface, aiding in the separation and interaction of surface charges. Wang *et al*.[7] introduced a nanoscale compound called DSPE-PEG2000-coated barium titanate nanoparticle (P-BTO), exhibiting increased surface charge disparity when subjected to ultrasonic light. This catalyzes the simultaneous production of ROS and O_2 *via* a REDOX reaction. The resultant oxygen significantly reduces low oxygen levels in the tumor milieu by decreasing HIF-1α, whereas reactive oxygen species adeptly eliminate cancer cells and block their spread. Assessments utilizing the thiazolium blue ammonium tetrabromoide assay and red blood cell hemolysis test showed significant biocompatibility across both living entities and lab environments. Near-infrared fluorescence imaging techniques uncovered a primary pattern in fecal excretion. When P-BTO is present in the bloodstream, mice exhibiting lower Ba levels are expelled *via* urine. Alterations to the BTO structure are recommended to tackle this issue and increase ROS generation efficacy. Zhou *et al*.[10] introduced a unique piezoelectric Tetragonal (T-BTO) type, discovered to stimulate a piezoelectrically sensitive polarized internal electric charge. By continuously separating and gathering electrons and holes, there was an improvement, resulting in a change in the conduction and valence bands towards energy levels suitable for producing O_2^- and OH radicals. This advancement led to the removal of cancer cells and the eradication of remaining tumors. The combination of biological nanoparticle injection and a hot gel reduced the viability of 4T1 cells to 12.6 %. In mice with 4T1 tumor xenografts, all treated mice exhibited an extended lifespan of over 40 d without recurrence, demonstrating a positive tumor-killing effect.

T-BTO showed minimal cytotoxicity *in vitro* and favorable biosafety *in vivo*, validated by CCK-8 assays and histological sections stained with hematoxylin and eosin. However, considering factors like crystallinity, defects, and size is crucial when adjusting morphology for piezoelectric polarization. Surface defect engineering, particularly focusing on point defects, can enhance catalytic activity and material stability. Modifying atomic coordination, electronic structure, and surface properties improves carrier mobility and conductivity. Wang *et al*.[7]. pioneered the use of oxygen defect engineering to create bismuth-doped oxygen-deficient barium titanate. This innovative approach led to a reduction in the band gap, while the modification with Bismuth (Bi) nanoparticles facilitated the formation of Schottky junctions, thereby enhancing carrier transfer and separation. This suppression of recombination under ultrasonic irradiation led to an enhancement in the efficiency of SDT against ovarian cancer. Additionally, the nanoparticles displayed a significant down-regulation effect on tumor-related genes and information. The creation of heterojunctions primarily involves the integration of materials with differing band gaps, resulting in improved carrier separation and transfer. Heterojunctions, crafted to enhance catalytic performance, encompass diverse types including metallic piezoelectric semiconductors, Z type heterojunctions, II type, and P-N type[24]. Among these, metallic piezoelectric semiconductor heterojunctions are the most common. Heterojunctions utilize the unique work operations and Fermi levels in metals and piezoelectric semiconductors to create Schottky barriers at an interface. When subjected to mechanical pressures such as ultrasound, a piezoelectric semiconductor creates a positive charged electric charge at the boundary. This procedure leads to a decrease in both the energy band and the Schottky barrier, facilitating effective electron movement between the piezoelectric semiconductor and the metal. This impedes the recombination of electron-hole pairs and fosters reduction reactions of ions. Zhao *et al*.[25] engineered Cu_2-XOBTONCs utilizing copper in transforming naturally occurring hydrogen peroxide into hydroxyl radicals for chemokinetic treatment. Studies conducted both *in vivo* and *in vitro* revealed substantial toxic effects and tumor suppression targeting resistant breast cancer in mouse models. Co-culturing with cells confirmed the low cell toxicity of the material. Including assessing mouse body weight, analyzing blood biochemistry, conducting blood routine tests, and examining visceral sections, verified the superior biocompatibility of Cu_2-XOBTONCs[25]. BTO functions as an acoustic enhancer for SDT and, when used alongside other kinetic treatments, as an enhancer, thus boosting the effectiveness in destroying tumors.

Piezoelectric catalytic immunotherapy:

The suppression of immune signals in tumors bears a complex connection to the Tumor Microenvironment (TME), marked by the heightened expression of various specific antibodies and chemokines. Within the field of immunotherapy, various strategies are devised to stimulate the immune system. The inescapable adverse reactions arising from unintended effects highlight the critical need for precise immunotherapy to ensure effective and minimally toxic treatment of tumors. LA, known for its excessive buildup in tumors, assumes a cruciform role the primary function in fostering immunosuppressive microenvironments within a wide range of signaling molecules. Henceforth, we propose a strategy for on-site catalytic activation of tumor immunity through catalytic oxidation/consumption of LA, serving as a sacrificial agent within the TME. Notably, hydrogen inhalation has demonstrated efficacy in enhancing systemic immunity in tumor patients while mitigating the toxicities associated with radiotherapy and chemotherapy drugs. Moreover, the continuous localized provision of Hydrogen (H_2) has been observed to incite immune responses at wound sites and facilitate wound healing, underscoring the immunomodulatory potential of H_2. The research unexpectedly uncovered the ability of H_2 to decrease the expression of Programmed Death-Ligand 1 (PD-L1) on specific tumor cells, including Hepa1-6 liver tumor cells. This finding indicates the potential for utilizing H_2 in tumor immunotherapy by locally activating the immune response within tumors. Although *in situ* photocatalyzed H_2 production at the tumor site holds promise for sustained tumor therapy, the limited tissue penetration of light poses challenges in treating deep-seated tumors. Here, an innovative approach is introduced, utilizing Ultrasound (US)-driven piezoelectric catalysis to generate hydrogen, with the aim of stimulating the immune response within deeply located tumors. Notably, H_2 possesses exceptional tissue penetration capabilities due to its small molecular size and low polarity. This allows it to readily infiltrate into tumors, thus promoting immune activation.

Recently, a two-dimensional Social Security Number (SSN) nano-catalyst has been developed to achieve US-driven piezoelectric catalytic immune activation in deep tumors. When stimulated by ultrasonic waves, SSN nanocatellators with piezoelectric properties demonstrated a precise level of control over the catalytic production of hydrogen and the oxidation/deprivation of LA. The *in vitro* and *in vivo* experiments collectively corroborate the efficacy of hydrogen molecules in diminishing PDL1 expression on Hepa1-6 cells. Lack of LA in tumors diminished T_{reg} cell activity, resulting in the activation of the tumor's immune reaction.

CHALLENGES AND FUTURE DIRECTIONS

In nanocatalysis medicine, piezoelectric catalytic medicine stands out as a unique branch. This field primarily focuses on utilizing oxidation-reduction reactions between oxygen and water molecules. This study's investigation and creation of piezoelectric catalytic substances underscore their significant promise in medical science, particularly in targeted tumor treatment. The development of high-performance piezoelectric materials is of great significance in the field of biomedical engineering. With the integration of artificial intelligence, piezoelectric material science, and biotechnology, it is expected to promote high-throughput screening of efficient piezoelectric catalytic materials, explore the mechanism of piezoelectric catalysis in drugs, and continue to optimize material design and manufacturing processes. Highly customizable piezoelectric catalytic materials can be integrated into artificial bioelectrical systems, providing new opportunities for monitoring and treatment. Through targeted modification, the design of novel piezoelectric materials can be developed in the direction of precise tumor therapy, which greatly promotes the application of piezoelectric catalysis in tumor therapy. Due to its unique flexibility, piezoelectric catalytic nanomaterials have shown extensive application potential in the medical field. Although the catalytic mechanisms of these materials have been explored using advanced techniques, their specific mechanisms of action *in vivo* still need to be further studied. Most studies explain medical effects by speculating on the material catalysis or the electric field effect generated by its surface charge, but the specific effects of nanomaterials and their piezoelectric catalysis on cells, tissues, and organs and the underlying mechanisms are still limited. Therefore, experimental and research applications of various biomarkers and imaging techniques will promote *in vivo* and real-time studies of the piezoelectric catalytic mechanism. Synergies with other therapies, due to the unique energy conversion properties of piezoelectric catalytic medicine, its combination with other clinical treatment modes has great potential. In conjunction with immunotherapy, the integration of piezoelectric materials endowed with elevated catalytic prowess presents a viable strategy. These materials facilitate the generation of ROS within the TME, culminating in the eradication of malignant cells and the elicitation of an immune-mediated response. Compared with traditional therapies that require high energy input, piezoelectric catalytic materials can stimulate ultrahigh reactivity with only slight stimulation, and can even obtain energy from human movement, a property that may greatly optimize and enhance the therapeutic effect. Furthermore, the induction of electron transfer by piezoelectric materials holds considerable significance in catalyzing specific biological reactions and the processes of biological signal transduction. This phenomenon serves to augment the therapeutic efficacy of interventions.

In general, piezoelectric catalytic materials have broad application prospects in the medical field, and through in-depth material design, mechanism research and synergistic studies with other therapies, it is expected to achieve more accurate and effective tumor treatment programs, providing a new direction for future medical treatment.

CONCLUSION

Piezoelectric semiconductor materials assume a pivotal role in SDT, showcasing their efficacy as ultrasonic sensitizers attributed to their exceptional physical robustness, favorable hydrophilic properties, heightened tumor-targeting capabilities, and ultrasonic piezoelectric responsiveness. Their capacity for ROS generation and biocompatibility constitute focal points warranting exploration, potentially bolstering their translational prospects in clinical settings. Presently, approaches such as material modifications and combination therapies are employed to enhance ROS efficiency. Despite the ongoing challenge of establishing a direct correlation between ROS generation efficiency and either the dosage or ultrasonic parameters of the acoustic sensitizer, current research underscore the promising efficacy of piezoelectric semiconductor acoustic sensitizers in tumor treatment. A more comprehensive grasp of the underlying principles of SDT and the pharmacokinetics of sensitizers is anticipated to facilitate the seamless transition of SDT techniques into clinical application.

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Conflict of interests:

The authors declared no conflict of interests.

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