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TERAHERTZ TECHNOLOGY IN TUMOR THERAPY: MECHANISMS, APPLICATIONS IN HEPATOCELLULAR CARCINOMA, AND FUTURE PROSPECTS

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Abstract: Terahertz(THz) technology, as a emerging non-ionizing electromagnetic wave therapy, has made significant progress in the field of tumor treatment in recent years. With its unique low-energy, non-ionizing characteristics and high sensitivity to biological tissues, THz technology can act on tumor cells without damaging normal cells and produce a series of biological effects, such as changes in cell membrane permeability, vibrations of protein molecules, and effects on telomeres and telomerase, thereby inhibiting tumor cell proliferation or inducing apoptosis. Compared with traditional surgery, chemotherapy, and radiotherapy, THz technology, with its high selectivity and low side effects, provides a safer and more precise treatment option for cancer patients. This review aims to summarize the latest advances in THz technology for tumor treatment, deeply explore its mechanisms of action, technical advantages, and clinical application prospects. At the same time, this paper will also analyze the current technical challenges, such as the penetration depth of THz waves, equipment costs, and optimization of treatment parameters, and look forward to further development of THz technology in tumor treatment in the context of multi-disciplinary integration, providing reference for related research and clinical applications.
Keywords: Terahertz; Non-ionizing characteristics; Protein molecular vibration; Low side effects

1 INTRODUCTION

Primary liver cancer(hepatocellular carcinoma, HCC) is one of the most prevalent and lethal malignancies worldwide, and its therapeutic efficacy is often limited by factors such as high tumor heterogeneity, drug resistance, and invasiveness. Traditional treatment modalities for liver cancer include surgical resection, chemotherapy, radiotherapy, and targeted drug therapy;however, these approaches continue to face significant challenges in improving patient survival rates [1]. In recent years, with the rapid advancement of biomedical technologies, terahertz(THz)radiation has emerged as a novel strategy offering innovative perspectives for liver cancer treatment. THz waves refer to electromagnetic waves with frequencies ranging from 0. 1 to 10THz, wavelengths from 30μm to 3mm, photon energies from 0. 4 to 41meV, and oscillation periods from 0. 1 to 10ps. As such, THz radiation falls within the far-infrared spectrum and is categorized as submillimeter wave radiation, bridging the gap between millimeter waves and infrared light. Notably, the frequency range of THz waves coincides with the vibrational, rotational, and intermolecular weak interaction frequencies of biological macromolecules, with corresponding energy levels lying within the THz band [2]. Due to its high sensitivity to biomolecules and water content, as well as its low ionization potential for biological samples [3], THz technology holds substantial promise for biomedical research and therapeutic applications. This review summarizes recent advances in THz-based antitumor research, including THz radiation-induced genomic alterations and phenotypic changes in tumor cells. Furthermore, we explore the potential of THz wave irradiation to influence cell division and its prospective application in cancer treatment.

2 MECHANISMS OF THZ IRRADIATION IN CANCER THERAPY

2.1 Impact on Cancer-Related Genes

DNA methylation, an epigenetic modification that does not involve alterations in the DNA sequence, plays a critical role in regulating gene expression. Aberrant regulation of gene expression is closely associated with carcinogenesis [4]. It has been reported that a strong correlation exists between carcinogenesis and abnormal DNA methylation at both single-gene and genome-wide scales [5]. Zhang et al. reported that STMN1 is highly expressed in hepatocellular carcinoma, and its expression level is closely related to patient prognosis [6]. Several CpG sites within the STMN1 gene in liver cancer exhibit methylation, and the methylation levels at these sites are negatively correlated with patient survival rates. Moreover, in liver cancer patients with high STMN1 expression, the expression of genes associated with m6A methylation modification is significantly increased. Additionally, a study by Lei et al. demonstrated that arginine methylation promotes glycolysis and tumor growth [7]. Selective use of methylation inhibitors effectively suppressed both glycolysis and tumor growth in relevant models.

THz demethylation is a photomedical technique that utilizes resonant THz radiation to dissociate methyl-DNA bonds and reduce global DNA methylation [8]. The characteristic energy of methylated DNA can be observed within the THz region. Therefore, THz radiation with appropriate intensity and frequency can alter the binding conditions of methylated DNA [3]. Studies have shown that under specific terahertz wave irradiation, the unwinding rate of DNA double strands increases [51], while receptor-ligand binding decreases [52]. To explore the potential of terahertz waves in regulating gene expression, Sun et al. investigated the effect of terahertz fields on histone-DNA affinity through molecular dynamics simulations [38]. In the absence of terahertz modulation, the binding free energy between the histone octamer and DNA was -728, 544kJ/mol, indicating an extremely strong interaction. When decomposed into four energy components, electrostatic interactions were found to be absolutely dominant, contributing -748, 744kJ/mol, while the other three components were relatively negligible. This is because the amino groups of lysine and arginine in histones are positively charged, whereas the phosphate groups in DNA are negatively charged; their electrostatic attraction dominates the binding interaction. Hydrogen bonds primarily exist in the form of N—H···O, suggesting that a light source resonating with N-H bond vibrations may alter related non-bonding interactions. When the nucleosome was irradiated with terahertz waves at 2746cm-1(3. 6μm), the binding free energy significantly decreased by 4, 206kJ/mol, indicating enhanced affinity within the complex. This enhancement mainly originated from changes in electrostatic contributions, with the electrostatic free energy decreasing by 4, 999kJ/mol in response to irradiation. Thus, terahertz waves at 3. 6μm hold great potential for regulating gene expression. THz demethylation is analogous to active demethylation. Extensive research has been conducted on abnormal DNA methylation in melanoma [9-11]. The underlying mechanism may be as follows: the resonance of the chemical bond between the methyl group and DNA in cancer DNA falls approximately within the 1. 6–1. 7THz range [3], which lies within the THz region. When methyl-DNA bonds are irradiated with THz waves at their intrinsic bond oscillation frequency, energy is preferentially absorbed by the bonding mode. High-power THz radiation with sufficient energy can disrupt methyl-DNA bonds through resonant excitation, thereby reducing the degree of methylation [4]. In another two-arm prospective study, Cheon et al. compared control and experimental samples of melanoma cells under demethylation conditions at 40μW for 30minutes [12]. The results showed that THz demethylation primarily occurred in CpG islands within genomic regions, where CpG sites(cytosine-guanine dinucleotide sites) appeared with high frequency. At CpG sites, the degree of gene demethylation was 53%, whereas at non-CpG sites, it was below 3%. Furthermore, THz-induced downregulation of cancer genes was associated with this demethylation effect. THz demethylation downregulated the FOS, JUN, and CXCL8 genes, which are involved in cancer and apoptotic pathways. The proteins encoded by FOS and JUN regulate differentiation, proliferation, and apoptosis, while CXCL8 is a major transcriptional and inflammatory factor in melanoma progression [13-15]. THz exposure upregulated these genes at 4hours, but their expression was significantly reduced after 24hours. This suggests that THz demethylation transiently stimulates transcription factors and gradually readjusts the aberrant overexpression of affected genes. The demethylation effect of THz has also been validated in blood cancer research. The degree of DNA methylation in leukemia was observed at a resonant feature of approximately 1. 7THz, and irradiation of blood cancer DNA samples showed that THz quantitative results were largely consistent with ELISA. Depending on the specific cancer cell line type, the degree of demethylation ranged from 10% to 70%, with most samples showing a substantial decrease in methylation. However, regarding lymphoma cell lines, SU-DHL1 and OCI-LY1 exhibited approximately twice the demethylation degree of SU-DHL9. Among T-ALL cell lines, CCRF-CEM and Jurkat showed significant differences [4]. In a study on colorectal cancer, it was found that terahertz pulses affected the expression levels of 442 genes, among which ALDH2 was significantly upregulated. Existing research has revealed through proteogenomic analysis of HBV-related HCC that liver-specific metabolic functions are impaired in HCC cells, with downregulation of ALDH1B1, ALDH2, and ALDH3B1 expression.

These findings collectively demonstrate that DNA demethylation occurs at specific THz resonant frequencies, and resonant high-power THz radiation can potently induce global DNA demethylation, with reduction rates varying across cell lines. THz demethylation holds promise as a modulator of gene expression and exhibits broad application prospects in liver cancer therapy. However, it is important not to overlook the issues revealed in these studies. The differences in DNA demethylation outcomes across various cell lines warrant further investigation. Additionally, the intensity and duration of THz irradiation require further exploration.

2.2 Impact on Cell Division

Actin filaments are major components of the cytoskeleton and play crucial roles in determining cell shape, motility, and division [16, 17]. Furthermore, the recent development of fluorescent probes has revealed that nuclear actin filaments are essential for transcriptional regulation, DNA repair, and gene reprogramming [18, 19]. The primary regulator of cytokinesis is the contractile ring, which is composed of actin filaments [20]. Huang et al. found that in hepatocellular carcinoma cells, loss of mitochondrial transcription factor A(TFAM) led to unexpected polymerization of nuclear actin [21]. The polymerization of nuclear F-actin is associated with the high metastatic capacity of liver cancer cells, and this polymerization significantly promotes liver cancer metastasis by altering chromatin accessibility and gene expression. This underscores the importance of nuclear actin as a potential therapeutic target. Additionally, a report by Liu et al. indicates that invasion and metastasis of liver cancer require significant cytoskeletal remodeling, making the dynamics of actin filaments a critical factor in the metastatic process of hepatocellular carcinoma [22]. The article points out that actin promotes the migration and metastasis of liver cancer cells by regulating the dynamic remodeling of the

cytoskeleton. Furthermore, circular RNA circASH2 inhibits the invasion and metastasis of liver cancer by suppressing tropomyosin alpha-4(TPM4), thereby weakening the stability of actin filaments.

Studies have found that during THz irradiation, cell division in the cell cycle arrests at mitosis. The underlying mechanism may be as follows:during the final stage of cell division, the contractile ring composed of filamentous actin(F-actin) normally disassembles;however, under THz irradiation, the contractile ring persisted for one hour [23]. In the study by Yamazaki et al. samples were irradiated for 60minutes with a relatively low peak power THz beam at 0. 46THz without beam focusing, with a peak power density of 0. 6W/cm², a duration of 10 milliseconds, and a repetition frequency of 1Hz [23]. The results showed that under THz irradiation, a characteristic cell morphology consisting of paired round cells was observed to persist for 60minutes, whereas control cells completed division within 15minutes [24]. Therefore, the persistence of paired round cells indicates that THz irradiation inhibits the progression of cell division. Meanwhile, in another study by Yamazaki et al. HeLa cells in an aqueous medium were exposed to THz irradiation at 80, 160, and 250μJ/cm² for 30minutes [25]. The results showed that samples irradiated at 80 and 160μJ/cm² exhibited dark areas in the cell cortex, indicating disassembly of actin filaments, with the number of actin filaments reduced by approximately 50% in the experimental groups. After irradiation at 250μJ/cm², actin aggregation occurred at the cell periphery. This suggests that THz irradiation causes disassembly of actin filaments, while high-intensity THz irradiation leads to actin filament aggregation near the cell periphery, which persists and causes cell division arrest. This is similar to the aggregation of actin filaments observed when chemical agents are deliberately used to disassemble them [26]. The disruption of actin filaments by THz irradiation suggests the possibility of optically controlling cellular functions. For instance, inhibiting actin polymerization reduces the migration and invasion of cancer cells [27]. A study by Hough et al. indicated that microtubules(MT) disintegrate within minutes following high-intensity THz pulses of picosecond duration, with the disintegration rate depending on THz intensity and spectral content [28]. The results showed that in the central region of THz irradiation, where the energy density reached 80μJ/cm², the most significant qualitative changes in MT structure were observed. Near the beam edge, 0. 5mm from the center, where the energy density decreased to 30μJ/cm², no significant structural changes were observed. Additionally, intense THz pulses substantially downregulated the expression of tubulin and other genes related to MT structure and function.

These findings indicate that THz radiation can inhibit cell division by disassembling tubulin and enhancing the formation and stabilization of actin filament assemblies in living cells. THz irradiation may be employed for optical manipulation of cellular functions through the regulation of actin dynamics. However, it is important to note that these studies were conducted in normal cells; the effects of THz irradiation on the proliferation and division of tumor cells remain to be further explored, and more work is needed to elucidate the underlying mechanisms of THz interactions.

2.3 Inhibition of Telomerase Activity and Reduction of Cancer Cell Migration

Telomeres are specialized DNA-protein complexes that function to protect and stabilize chromosomes. When telomeres shorten to a critical length and encroach upon the coding regions of DNA, cells undergo senescence, apoptosis, and DNA double-strand breaks. The expression of telomerase in cancer cells is a key factor underlying the infinite proliferation and long-term survival of most cancer cells [29-31]. Telomerase reverse transcriptase(TERT) is the catalytic subunit of telomerase. The telomerase complex plays a critical role in carcinogenesis through both telomere-dependent and telomere-independent mechanisms [50]. The overall incidence of TERT promoter mutations in hepatocellular carcinoma is 43. 9%(1831/4170), with a significantly higher mutation frequency in HCV-related HCC(64%) compared to HBV-related HCC (37%). TERT promoter mutations mainly occur at positions-124bp (G>A) and -146 bp (G>A), creating new binding sites for ETS transcription factor family members and leading to increased TERT expression [36]. Inhibition of telomerase activity has been reported as a potential therapeutic strategy for cancer [32, 33]. Currently, telomerase inhibitors have numerous limitations, including non-specific damage to cells due to low specificity, development of drug resistance with long-term use, limited applicability across all cancer types, and potential undisclosed toxic side effects [34, 35]. A study by Stroth et al. indicated that in the context of chronic liver disease and liver cancer, telomere shortening may trigger chromosomal breakage-fusion-bridge cycles, further leading to genomic instability and promoting tumor formation [36]. Telomerase reactivation is observed in over 80% of liver cancers and is considered a rate-limiting step in hepatocarcinogenesis. Telomerase reactivation stabilizes telomere function, providing a proliferative advantage to tumor cells. Telomerase is activated as early as the preneoplastic stage in regenerative nodules and cirrhosis, suggesting its early role in liver cancer development. Telomere shortening can induce genomic instability, while telomerase reactivation supports the infinite proliferation of tumor cells. Therefore, telomeres and telomerase represent potential therapeutic targets in liver cancer, and modulating telomere biology may effectively inhibit liver cancer progression.

Terahertz radiation is now widely regarded as a promising non-pharmacological and non-invasive electromagnetic intervention approach [37]. Its low photon energy characteristic ensures that THz radiation induces virtually no ionizing effects, thereby preserving genomic integrity [38]. In a study by Yin et al, molecular dynamics simulations of THz-irradiated cellular maps combined with cell biology analyses demonstrated that in two breast cancer cell lines (4T1 and MCF-7), long-term exposure to 33THz radiation with a power of 5mW and a spot diameter of 400μm(ensuring a consistent power density of 4W/cm²reaching the cells) inhibited telomerase activity [39]. The results showed that relative telomerase activity in the experimental groups was significantly reduced at 1, 2, 3, 7, 15, and 21hours post-irradiation compared to the control group, with the reduction becoming more pronounced as irradiation time increased. After 21 hours of THz treatment, relative telomerase activity decreased by 77% in 4T1 cells and 80% in MCF-7 cells.

This led to telomere shortening, triggering a telomere crisis and adversely affecting the survival of breast cancer cells. Irradiating mouse tumor cells with THz rays significantly inhibited breast cancer cell growth in vivo. These findings suggest that prolonged THz treatment can reduce telomerase activity in 4T1 and MCF-7 cells and maintain it at low levels. The percentage of senescent cells increased significantly, reaching 42% after 7hours of THz irradiation and 56% after 15hours. Subsequent research revealed that irradiation at 34THz and 34. 5THz resulted in a significant increase in relative telomerase activity, indicating that the regulation of telomerase activity may be frequency-specific. Furthermore, the research team investigated the effect of short-term THz exposure on the migratory capacity of cancer cells. The results showed that compared to cells not exposed to THz, the migratory capacity of both cell types was inhibited after 3hours of exposure. These results indicate that short-term THz exposure strongly suppresses cell proliferation and migration. A study by Sun et al. also explored the effect of THz irradiation on the migratory capacity of tumor cells [38]. Molecular dynamics simulations revealed the effects of optical radiation at a specific wavelength of 3. 6μm(equivalent to 83THz). Cellular functional assays demonstrated that low-power 3. 6μm THz waves successfully inhibited cancer cell migration by 50% and reduced glycolysis by 60%. Additionally, applying 3. 6μm THz radiation to HCT-116 cancer cells in a xenograft mouse model with metastasis induced by splenic injection resulted in a 60% reduction in liver metastasis, successfully validating the inhibitory effect of THz on cancer cell migration in vivo.

The aforementioned studies demonstrate that under THz irradiation for a certain duration. telomerase activity in tumor cells is significantly reduced. tumor growth is inhibited. and the migration of tumor cells is suppressed. In the context of chronic liver disease and liver cancer. telomere shortening may trigger chromosomal breakage-fusion-bridge cycles. further leading to genomic instability and promoting tumor formation. Telomerase reactivation is present in over 80% of hepatocellular carcinoma(HCC) cases and is considered a rate-limiting step in hepatocarcinogenesis. Telomerase reactivation stabilizes telomere function. providing a proliferative advantage to tumor cells [36]. THz irradiation provides a theoretical basis for liver cancer therapy and holds potential application prospects. However. substantial experimental data are still needed to substantiate the effects of THz on telomerase and to determine whether THz possesses genotoxicity.

2.4 Conclusion

The above findings indicate that exposure to appropriate THz irradiation can not only induce DNA demethylation but also disassemble tubulin,enhance the formation and stabilization of actin assemblies in living cells,and simultaneously affect telomerase activity in tumor cells,leading to its downregulation.These effects contribute to tumor treatment through the regulation of gene expression via demethylation,inhibition of cell division,and reduction of tumor cell migration.However,substantial experimental evidence is still required to substantiate the effects of THz on tumors and to elucidate the underlying mechanisms of THz action.

3 LIMITATIONS OF THZ IRRADIATION THERAPY

With the development of THz technology. industrial and medical applications have been proposed in recent decades. The potential toxicity of THz radiation to human health has also garnered significant interest among researchers in this frequency range [40]. Interactions between THz radiation and biological systems have been previously investigated. Two international projects on electromagnetic fields. the European THz-BRIDGE and SCENIHR projects [41]. have summarized recent research on the biological effects of THz radiation. For instance. THz irradiation can inhibit cell proliferation and alter the adhesion properties of neural cell membranes. Other studies have shown that THz induces DNA destabilization [42-44]. leading to chromosomal aberrations in human lymphocytes [45]. It has been reported that THz irradiation can activate wound response genes in mouse skin and induce DNA damage in artificial three-dimensional human skin tissue models [46, 47]. Research by Yamazaki et al. indicates that THz wave energy can propagate over 1000μm in aqueous solutions [25]. meaning that the photon energy from irradiation is converted into pressure energy. disrupting cellular actin filaments in culture. Once THz photon energy is absorbed on the human surface. it is converted into thermal and mechanical energy. Pulses generate shock waves on the surface of liquid water [48]. These generated shock waves can propagate to depths of several millimeters. Similar phenomena may also occur in the human body. Shock waves induced by THz radiation could impose mechanical stress on biomolecules and alter their conformation. This result aligns with previous studies showing that shock waves generated by piezoelectric ceramic vibrators can induce actin filament disruption [49]. Shock waves with a peak pressure of 16MPa focused on cultured cells disrupted the cell cortex and filopodia. Therefore. shock waves produced by THz irradiation can penetrate deep into biological tissues. thereby altering cellular protein conformations. THz irradiation affects not only the human body surface but also penetrates several millimeters deep into tissues. This penetrative effect should be considered when establishing safety standards for high-power THz radiation. These results also suggest that THz irradiation could be employed for non-invasive manipulation of cellular functions by modulating actin filaments. Further research on the effects of THz irradiation on biological dynamics is still needed for the technological development of THz frequencies.

In the biomedical field, although THz technology offers unique advantages such as non-invasive imaging, high sensitivity, and potential for biomolecular recognition, its application still faces certain limitations, particularly in the context of liver cancer therapy:(1)High water absorption. Biological tissues contain substantial amounts of water, and water exhibits an extremely high absorption rate for THz waves, leading to signal attenuation and consequently reducing image quality and diagnostic accuracy. This high absorptivity also limits the effectiveness of THz waves in

real-time monitoring and therapeutic processes. (2)Unclear biological effects. The long-term biological effects of THz waves on biological tissues are not yet fully understood. Although existing studies have indicated safety at low energy levels, potential biological impacts may exist at higher powers or with prolonged exposure. This uncertainty restricts the application of THz technology in clinical treatment, especially in therapies involving sensitive organs such as the liver. (3)Insufficient clinical experience. There is limited clinical experience and data regarding THz technology, particularly in liver cancer treatment. Current research is predominantly concentrated in laboratory and preliminary clinical stages, and widely accepted treatment standards or protocols have yet to be established. Due to the aforementioned reasons, THz technology in liver cancer management is primarily utilized for early diagnosis, tumor boundary detection, and surgical assistance, rather than direct therapeutic intervention. Future advancements may require significant breakthroughs in areas such as biocompatibility, imaging resolution, and clinical validation before broader application in liver cancer treatment can be achieved.

Furthermore, focused THz radiation may exceed the energy threshold of 80μJ/cm², thereby altering actin structures. Therefore, the biological effects of THz radiation mediated by shock waves must be considered when establishing safety standards. The effects of THz radiation on the skin surface have been studied and summarized [41]. Improving the safety of THz irradiation and reducing damage to normal tissues are critical challenges that need to be addressed in THz therapy. The specific intensity and duration of THz irradiation require further investigation, as do the potential hazards associated with post-irradiation exposure.

4 PERSPECTIVES

Currently, cancer treatment modalities are advancing rapidly, and the application prospects of THz radiation encompass both non-invasive diagnostics and the modulation of distinct metabolic processes within tissues. As a non-pharmacological, non-invasive electromagnetic radiation with low photon energy, THz has been demonstrated within safe thresholds to possess therapeutic potential against tumors. Its characteristics enable the detection of vibrational modes of proteins, nucleic acids, and other biomolecules in tumor cells, allowing for the identification of abnormalities in tumor cell metabolism, signal transduction, and growth cycles. This provides a basis for the development of novel targeted therapeutic agents. In the future, through in-depth investigation of the interactions between THz waves and hepatocellular carcinoma cells, a better understanding of the mechanisms underlying liver cancer occurrence and progression can be achieved, facilitating the development of new diagnostic and therapeutic approaches. With continuous technological advancements and multidisciplinary collaboration, THz technology is expected to play a significant role in early diagnosis, personalized treatment, and long-term prognostic assessment of liver cancer, thereby advancing the development of precision medicine in this field. According to existing literature, in addition to studies on clearly demonstrated mechanistic effects, cellular research should focus on high-intensity THz to explore its potential hazards to biological samples. Furthermore, animal experiments assessing genotoxicity, carcinogenicity, and teratogenicity are necessary to expand and improve the available data for risk assessment. Currently, comprehensive molecular mechanism studies elucidating the effects of THz irradiation on various biological processes in tumors are lacking. More research is needed in the future to validate the feasibility and efficacy of THz.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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