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Noninvasive Promotion of Neuronal Differentiation in Human Neural Progenitor Cells Using Terahertz Wave Illumination

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ABSTRACT

Recent advances in neuromodulation have demonstrated the importance of precise and minimally invasive strategies for modulating neuronal function. Terahertz (THz) wave has emerged as a promising method due to its low photon energy and ability to interact with biomolecular vibrational modes without inducing ionization. These frequency-specific interactions can affect water dynamics around biomolecules, modify molecular interactions, and alter cellular signaling processes that influence neuronal responses. In this study, the effects of THz irradiation on the differentiation of human neural progenitor cells in terms of safety and enhancement are investigated. Cellular safety is assessed using viability assays, live/dead imaging, and expression analysis of stress-related genes. All of these results indicate absence of cytotoxic effects after THz exposure. Concurrently, the THz irradiation significantly promotes neuronal differentiation, evidenced by lower levels of stemness markers (SOX2, Nestin) and higher levels of neuronal markers (β3-tubulin, GAP43) in both quantitative Polymerase Chain Reaction (qPCR) and immunocytochemistry (ICC). Morphological analyses further reveal enhanced neurite-associated structures in THz-exposed cells. These findings collectively indicate that THz irradiation can alter neuronal differentiation while maintaining cellular integrity. Such properties suggest THz exposure as a promising noninvasive tool for modulating neural development and function.

1 | Introduction

Neuromodulation is essential in advancing our understanding of how neural circuits operate and in developing treatments for neurological disorders. By enabling precise control of neuronal activity, neural stimulation allows researchers to investigate how neurons generate, process, and transmit information, providing insight into brain function and supporting the development of therapeutic strategies for neurological disorders [1–3]. Recent Tetrahertz (THz) neuromodulation studies have shown that the nervous system is a highly sensitive and responsive biological network, in which even slight external physical stimuli can alter membrane properties, ion dynamics, and structural–functional interactions of neurons [2, 4, 5].

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A variety of neuromodulation approaches have been developed, each capable of influencing neural activity with distinct spatial reach and temporal resolution [1]. Noninvasive brain stimulation techniques such as transcranial magnetic stimulation, transcranial current stimulation, and transcranial ultrasound stimulation can modulate cortical excitability without surgical intervention, but their millimeter-level spatial precision limits the ability to target specific neuronal populations. In contrast, deep brain stimulation transmits electrical pulses to deep nuclei through implanted electrodes and provides strong clinical benefits, yet its invasiveness and limited spatial selectivity remain major challenges [6–9]. These methods show the capability of external physical stimuli to modulate neural circuits, and they emphasize the need for neuromodulation approaches that offer precise, minimally invasive control. These limitations have increased interest in THz waves as a promising approach for achieving noninvasive and precise neuromodulation.

The THz wave lies between microwave and far-infrared and resonantly couples with vibrational modes of biomolecules, including hydrogen bonding and dipole reorientation [10, 11]. Its low photon energy provides opportunities for nondestructive biomedical modulation and label-free biosensing. Recent reviews have highlighted rapid advances in THz-based biochemical sensing and metasensing platforms, emphasizing improvements in sensitivity, molecular specificity, and integration with microfluidic and photonic technologies [12, 13].

For THz biomedical applications, there have been numerous researches on cell modulation via THz wave and reporting various effects on cells, while leaving its modulation mechanisms rarely debated [14–19]. Among them, several studies have suggested that the biomodulation could be attributed to interaction with molecular resonance. Series of THz irradiation studies on human cancer cell line have demonstrated THz manipulation of DNA methylation level [20, 21]. In those studies, broadening resonance mode in methyl group is suggested to be responsible, which is located near 1.6 THz [22]. More recently, metasurface-based spectral filtering has been used to interrogate the contribution of selected frequency bands within broadband THz radiation [23]. These findings motivate further investigation whether frequency-dependent interactions may also play a role in other cell line, including neuronal models.

Neurons are highly sensitive to these physical fluctuations, most notably in their membrane excitability and cytoskeletal reorganization. These changes include altered ion balance, modified membrane potential, and shifts in neurite growth and synaptic protein expression [24, 25]. Overall, these effects suggest that THz wave can influence neuronal differentiation by modulating membrane dynamics and intracellular signaling pathways to promote neurite extension and differentiation.

In this study, we used THz wave to investigate its effect on the differentiation of human neural progenitor cells. Experiments were designed to determine whether the THz irradiation can promote neuronal differentiation while maintaining cellular viability. Human neural progenitor cell line derived from the ventral mesencephalon (ReNcell VM) was chosen as the model system because it is an immortalized ventral mesencephalic progenitor line with stable growth and robust differentiation into neurons. These properties make it a widely adopted platform for studying human neurodevelopment and neuronal behavior [26]. To assess cellular safety and exclude potential cytotoxic effects, we evaluated cell viability, stress-related gene expression, and live/dead responses following THz exposure. We then examined THz-induced neuronal differentiation by quantifying stemness markers and neuronal markers, including SOX2, Nestin, β3-tubulin, and GAP43, using qPCR. Morphological changes associated with differentiation were further analyzed through neurite-related immunostaining.

2 | Experimental Section

2.1 | THz Irradiation Setup and Experimental Configuration

To expose ReNcell VM to intense THz waves, a home-built THz-TDS system was used, as depicted in Figure 1a. A Ti: Sapphire regenerative amplifier (Spitfire Ace, Spectra-Physics) delivers 35 fs near-infrared pulses at 1 kHz repetition rate with pulse energies of 5 mJ. High-power THz pulses were generated via optical rectification scheme employing tilted-pulse-front pumping in a $LiNbO_3$ crystal, delivering a pulse energy of 2 μJ with spectral range of 0.1–3 THz [27]. The THz pulse repetition rate is 1 kHz, which is identical to that of the pump laser. The THz pulse power could be controlled using a pair of wire-grid polarizers. THz power was fixed during the experiment. The THz wave was guided by a set of off-axis parabolic mirrors, focused onto the sample with spot diameter of approximately 0.5 mm. The beam spot size was estimated via knife-edge method. The corresponding average power density at the beam spot was estimated as 1 W/cm^2. THz electric field in time domain was measured via electro-optic sampling with a 500-μm-thick ZnTe (110) crystal. Its temporal waveform illustrated in Figure 1b was Fourier-transformed to obtain corresponding spectral profile, depicted in Figure 1c. Whole experiments were performed under dry air condition to minimize water absorption.

The experiments were performed in vertical geometry so that the THz wave propagates upward through dry air and reach the cells without suffering significant attenuation by culture medium. For gene expression analysis, pelletized cells located at the bottom of the Eppendorf tubes (EP tubes) were filled with the culture media (Figure 1d). Therefore, the THz pulses are focused on the bottom of the EP tube. For optical and imaging-based assays, well-plate-seeded cells were used. An incubating chamber (Okolab) was used to maintain the sample environment at 37°C with humidified CO_2 (5%)/air mixture flow. (Figure 1e) An optical microscope was used to monitor the status of ReNcell VM (Figure 1f) during THz irradiation.

2.2 | Cell Culture and Differentiation of ReNcell VM

Human ReNcell VM neural progenitor cells were cultured on 100 mm tissue culture dishes pre-coated with laminin (20 μg/ml, 4 h, 37°C). Cells were maintained in proliferation medium supplemented with epithelial cell growth factor (20 ng/ml)

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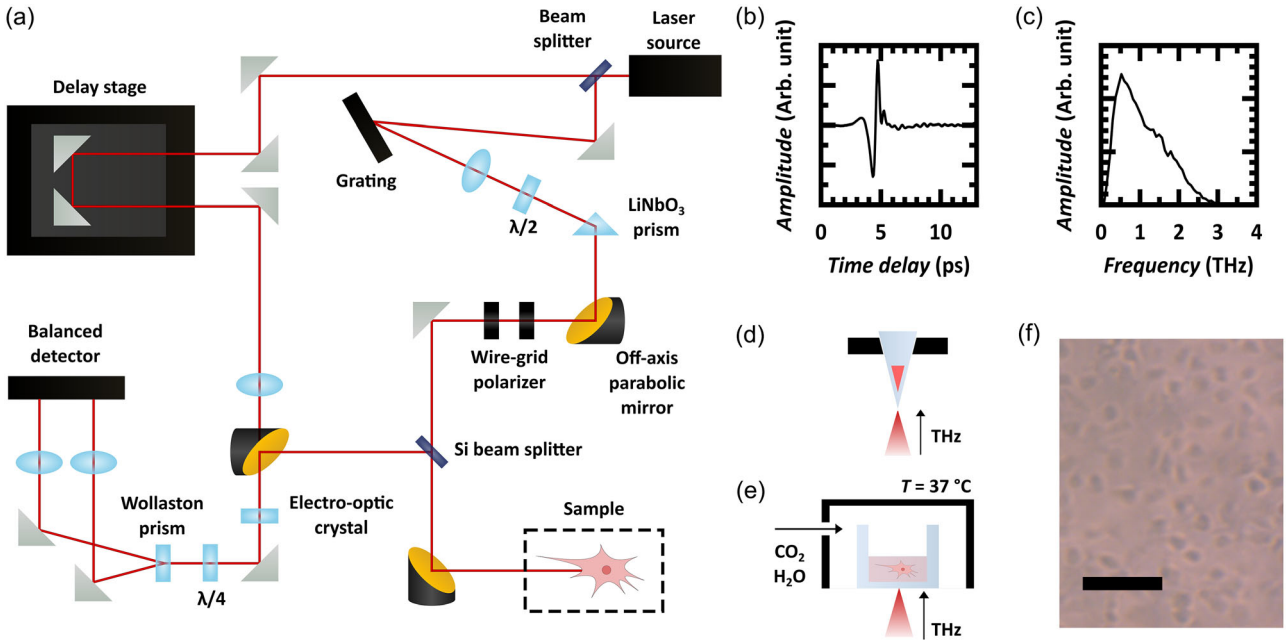

FIGURE 1 | Experimental configuration of THz irradiation on ReNcell VM. (a) THz-TDS setup. Dashed box indicates the location of the sample. (b,c) Temporal waveform of the generated THz electric field and its frequency spectrum. (d,e) THz exposure schemes for the ReNcell VM sample pelletized in an EP tube and cultured in a well plate, with atmosphere and temperature control in the well plate condition. (f) Optical microscope image of ReNcell VM in well plate. Scale bar, 100 μm.

and fibroblast growth factor (20 ng/ml) in a humidified incubator (37°C, 5%, CO_2). Cells were cultured upon reaching 80%–90% confluency. For neuronal differentiation, the proliferation medium was replaced with differentiation medium 48 h prior to THz exposure. The differentiation medium was refreshed every 24 h throughout the experimental period to ensure stable differentiation conditions.

2.3 | Evaluation of THz Wave-Induced Cytotoxicity and Cellular Stress Responses

To evaluate potential cytotoxicity of THz exposure, ReNcell VM cells were seeded into 96-well plates (5,000 cells/well) and incubated overnight for cell attachment. Cells were then exposed to THz radiation for 15, 30, and 45 min ($n = 3$ per condition). Cell viability was quantified using the Cell Counting Kit-8 (CCK-8) according to the manufacturer's protocol. Following the addition of 10 μl CCK-8 reagent, cells were incubated for 2 h at 37°C, and absorbance at 450 nm was measured using a microplate reader. Viability was normalized to nonirradiated controls.

Live/dead staining was performed on well-plate-seeded cells using LIVE/DEAD cell Imaging Kit (488/570, Invitrogen). Reagents were thawed at room temperature, mixed to prepare a 2x staining solution, and added directly to the culture medium. Cells were incubated for 15 min at 20°C–25°C in the dark and subsequently imaged.

For the assessment of stress-related gene responses, pelletized ReNcell VM were used. The pelletized cells were maintained in culture medium supplemented with HEPES buffer (10 mM) to maintain physiological pH. Following THz exposure, total RNA was extracted using the RNeasy Mini Kit (Qiagen). Complementary DNA (cDNA) was synthesized using the Superscript VILO cDNA Synthesis Kit (Invitrogen), and gene expression of heat shock protein 90 (HSP90) and C-reactive protein (CRP) was quantified via qRT-PCR using SYBR premix Ex Taq (TaKaRa).

2.4 | Quantitative Gene Expression and Marker Immunostaining

Total RNA was isolated from pelletized cells after THz irradiation using the RNeasy Mini Kit and reverse-transcribed from 2.5 μg RNA using the VILO cDNA Synthesis Kit. qRT-PCR was performed using SYBR premix Ex Taq on a real-time PCR system (Applied Biosystems). Each 20 μl reaction contained 10 μl master mix, 10 μM gene-specific primers, and 50 ng cDNA. Primer sequences for β3-tubulin, growth Associated Protein (GAP43), Nestin, SOX2, HSP90, CRP, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) are listed in Table S1. All samples were analyzed in triplicate. Relative expression levels were calculated using the ΔΔCt method normalized to GAPDH.

For immunostaining, cells cultured in well plates were used. At 24 h after THz irradiation, cells were washed with Dulbecco's Phosphate Buffered Saline and fixed with 4% paraformaldehyde for 10 min at room temperature. Permeabilization was performed using 0.1% Triton X-100 for 10 min. After blocking for 1 h at room temperature, cells were incubated with primary antibodies against β3-tubulin (1:500, Abcam) or Nestin (1:100, Invitrogen) for 2 h. Secondary antibodies (Alexa Fluor 488 and 594 conjugated IgG; 1:500, Invitrogen) were applied for 1 h in the dark. Nuclei were counterstained with 4′, 6-diamidino-2-phenylindole (DAPI) (5 min). Fluorescence images were acquired with

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identical exposure parameters across all conditions to ensure comparative analysis.

2.5 | Statistical Analysis

Significant differences between the control and THz groups were analyzed by One-way ANOVA followed by Tukey's post hoc test using Origin. A p-value of <0.05 was considered statistically significant. Data are presented as mean ± standard error of the mean (SEM).

3 | Results and Discussion

3.1 | Cytotoxicity and Stress Evaluation After THz Exposure

To establish a basis for evaluating the biological effects of THz irradiation on ReNcell VM, we first assessed whether the applied THz exposure induces any cytotoxicity under our experimental conditions. Although THz waves are nonionizing, several studies have indicated that high-intensity THz waves may alter membrane permeability or activate stress-related pathways. Such responses could interfere subsequent analyses by making it difficult to distinguish THz-induced biological effects from nonspecific cellular stress or damage. Therefore, verifying the biological safety of our irradiation conditions was a necessary step before proceeding with further experiments.

To determine whether THz exposure affects cell viability, CCK-8 assays were performed after 15, 30, and 45 min of irradiation. Metabolic activity remained unchanged across all three exposure durations in Figure 2a. These results indicate that short-term THz irradiation does not reduce cell viability. Based on these results, we fixed the irradiation duration at 1 h for all following experiments.

We next assessed stress-related transcriptional responses following 1 h of THz exposure. HSP90 and CRP were examined as representative markers of cellular stress and early inflammatory responses. HSP90 was selected as a representative heat shock marker because it is a well-established molecular chaperone that is rapidly upregulated in response to elevated temperature and protein misfolding-associated stress and is commonly used to assess activation of the cellular heat shock response under mild thermal stress [28], while CRP is commonly associated with inflammation-related signaling [29, 30]. These genes were selected to evaluate whether THz irradiation activates stress-responsive transcriptional pathways. No significant differences in gene expression were observed in Figure 2b. Statistical analysis of the qPCR data was performed using one-way ANOVA followed by Tukey's post hoc test, with a significance threshold

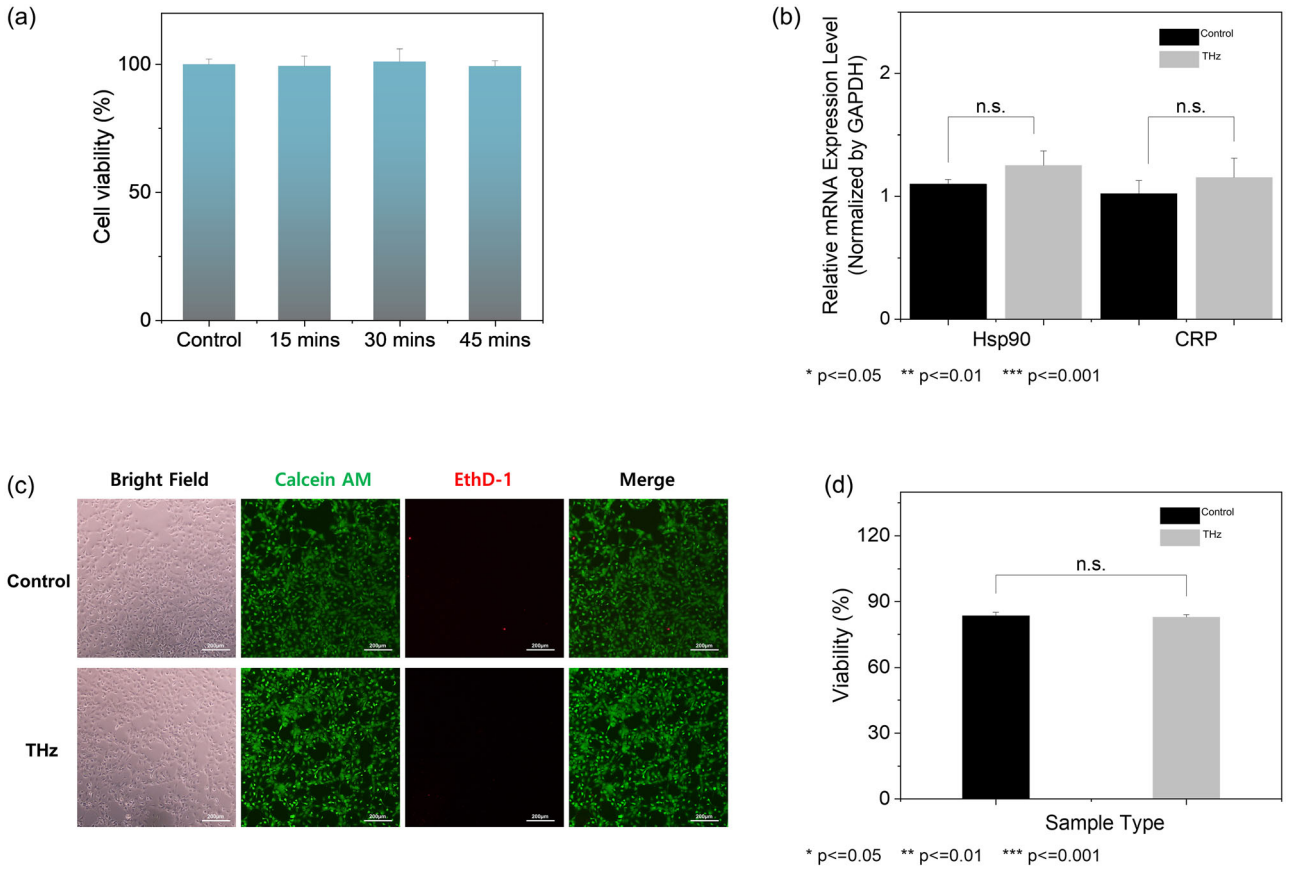

FIGURE 2 | Evaluation of cytotoxicity and stress responses following THz irradiation. (a) Cell viability assessed by CCK-8 after 15, 30, and 45 min of THz irradiation. (b) qRT-PCR analysis of HSP90 and CRP expression following 1 h of THz exposure. (c) Live/dead fluorescence imaging performed after 1 h of THz irradiation. (d) Quantification of live/dead fluorescence ratio. Data represent mean ± SEM from three independent experiments.

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of $p < 0.05$. All comparisons showed no significant changes and were labeled ns.

Live/Dead fluorescence imaging was subsequently conducted to examine membrane integrity following 1 h of THz exposure. Calcein-Acetoxymethyl Ester (AM) produces green fluorescence in cells with intact membranes and active intracellular esterases, whereas Ethidium Homodimer-1 (EthD-1) selectively enters membrane-compromised cells. THz-irradiated cells displayed strong Calcein-AM signals with minimal EthD-1 signals in Figure 2c, indicating that the irradiation did not induce membrane disruption. Quantification of the Live/Dead fluorescence signals was used to assess cell viability in Figure 2d.

3.2 | THz Irradiation Enhances Neuronal Differentiation in ReNcell VM

With no cytotoxic or stress responses detected, we next evaluated whether THz exposure modulates neuronal differentiation in ReNcell VM. Neural progenitor differentiation proceeds through the reduced expression of stemness markers, accompanied by the induction of neuron-related genes. To examine whether THz irradiation influences these differentiation processes, we quantified the mRNA expression of Nestin, SOX2, β3-tubulin, and GAP43 following 1 h of THz exposure.

As shown in Figure 3a, both Nestin and SOX2 transcripts were significantly decreased after THz irradiation. Nestin encodes an intermediate filament (IF) protein associated with neural progenitor characteristics, and SOX2 is a key transcription factor that maintains stemness and self-renewal [31, 32]. The reduction of these two markers indicates a loss of progenitor-like features. In contrast, β3-tubulin expression was markedly increased following THz exposure. Because β3-tubulin represents a structural component of immature neurons, its increased expression indicates a shift toward neuronal differentiation [33]. GAP43, a gene strongly associated with neurite extension and axonal growth, was also upregulated, indicating increased cytoskeletal reorganization and early neuronal maturation [34]. Altogether, these transcriptional changes indicate that THz irradiation promotes a shift toward neuronal phenotype.

To evaluate protein-level changes and morphological features associated with differentiation, we performed ICC for Nestin and β3-tubulin. β3-tubulin-positive cells increased substantially after THz exposure, with more extensive and dense neurite structures compared with control group in Figure 3b. Consistent with this morphological change, β3-tubulin mRNA was upregulated after THz irradiation, and quantitative ICC analysis further confirmed a significant increase in β3-tubulin immunofluorescence intensity in Figure S1. In contrast, although Nestin transcripts decreased following THz exposure, Nestin immunostaining did not show a corresponding decrease. This difference reflects both marker-specific characteristics, which are influenced by total protein abundance, subcellular localization and cytoskeletal organization [35].

Nestin is an IF, which forms structurally stable filament networks and exhibit relatively long protein lifetimes compared to its transcripts [36, 37]. Therefore, a reduction in Nestin transcription may not immediately translate into a measurable decrease in ICC intensity at a single examined time point. By contrast, β3-tubulin is associated with highly dynamic microtubules that undergo rapid remodeling during neuronal differentiation. This can lead to prompt changes in β3-tubulin distribution and microtubule organization, which can contribute to enhanced ICC signals [38, 39]. The significant upregulation of β3-tubulin mRNA observed by qPCR supports that the enhanced ICC signal reflects genuine transcriptional upregulation rather than only a redistribution effect. DAPI staining showed comparable numbers of nuclei between THz-irradiated and control groups in Figure 3b, indicating that the increase in β3-tubulin reflects neuronal differentiation rather than differences in cell density.

Overall, the combined qPCR and ICC results demonstrate that 1 h of THz irradiation promotes neuronal differentiation in ReNcell VM, as evidenced by the downregulation of progenitor-associated genes (Nestin and SOX2) and the strong upregulation of neuronal and neurite-related markers (β3-tubulin and GAP43). Although Nestin protein levels did not fully parallel

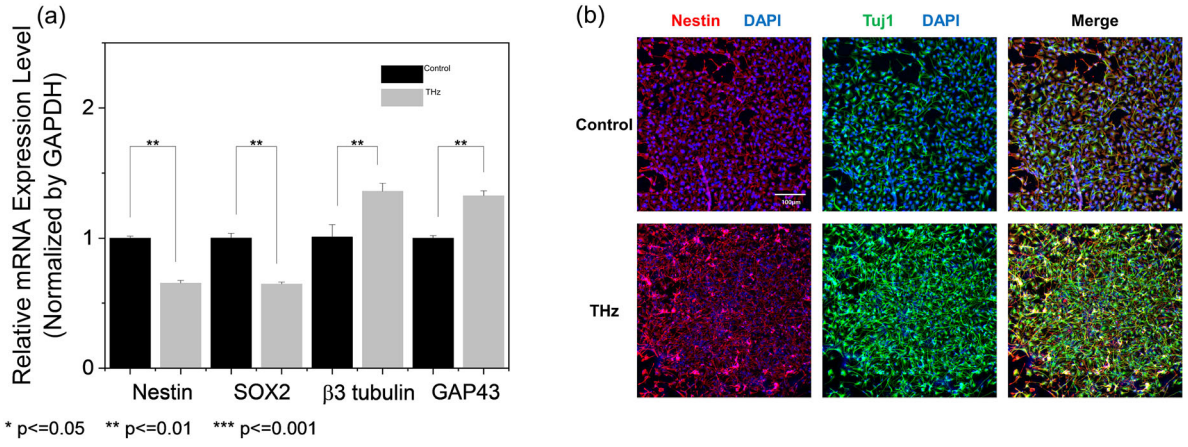

FIGURE 3 | THz irradiation promotes neuronal differentiation in ReNcell VM. (a) qRT-PCR analysis of Nestin, SOX2, β3-tubulin, and GAP43 expression following 1 h of THz irradiation ($n = 3$, ** $p \leq 0.01$). (b) ICC for Nestin, β3-tubulin, and DAPI staining. Data represent mean ± SEM from three independent experiments.

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its transcriptional decrease, the marked increase in β3-tubulin at both the molecular and morphological levels indicate accelerated progression toward a neuronal phenotype. Previous studies suggest that THz wave can modulate membrane excitability and cytoskeletal signaling, and such biophysical effects may contribute to the differentiation shift observed in this study [40–43].

4 | Conclusion

In summary, this study demonstrates that biologically safe THz irradiation can act as a potent biophysical stimulus that promotes neuronal differentiation in human neural progenitor cells. In the absence of cytotoxic or stress responses, THz exposure promoted transcriptional and structural changes. These changes included the downregulation of progenitor markers and the induction of neuronal markers. THz stimulation increased β3-tubulin expression, enhanced neurite outgrowth, and upregulated GAP43. These changes indicate accelerated early neuronal maturation at both molecular and morphological levels. These findings suggest that THz irradiation can alter cellular behavior through physical mechanisms, rather than through typical biochemical signaling pathways. Although the precise biophysical mechanisms remain unresolved, prior studies suggest several pathways through which THz wave may influence gene regulation. Proposed mechanisms include THz-induced alterations in transcription-factor interactions, resonance-driven changes in DNA breathing and base-pair vibrational modes, and enhanced Ca^{2+} influx via increased permeability of voltage-gated calcium channels [44]. These pathways provide a reasonable biological basis that is consistent with the transcriptional and differentiation related changes we observed following THz exposure in ReNcell VM. Overall, this work establishes a foundation for THz-based modulation of neuronal differentiation and shows the broader potential of THz wave as a noninvasive, contact-free modality for regulating cell fate.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

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