Terahertz Stimulate Specific Signaling Pathways in Human Cells

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***Abstract*—Terahertz (THz) waves can influence gene expression and consequently could affect the cell phenotypic properties. In this study, we evaluated the cell response of human cells exposed to THz radiation. We show that 2.52 THz frequency alters the expression of specific messenger ribonucleic acids (mRNAs), microRNAs and intracellular signaling pathways, which were not observed in a thermally-matched bulk-heating control.**

I. INTRODUCTION

In recent years, many THz imaging and sensing technologies have been developed, which have revolutionized the landscape of this rapidly evolving research discipline. These innovative technologies are now finding increasing use for a host of applications. A few examples include medical and biological imaging, security screening, quality control of food and pharmaceuticals, ultrafast computing, and wireless communication [1]. The emergence of these new THz-based applications has resulted in an increased interest in the biological effects associated with this frequency range. To date, several investigations have been performed to better understand the bioeffects generated from THz radiation. The data from these reports indicate that THz can exert a diverse range of effects at the organism, tissue, and cell level [1]. It is reported that THz waves can directly impact the structure, functional activity, and dynamics of Deoxyribonucleic acid (DNA) and proteins. Thereby, THz radiation can significantly influence gene expression and consequently can affect the biochemical and phenotypic properties of the exposed cells. In fact, recent studies demonstrated that THz radiation can cause gene transcriptional alterations in various cell types [2], [3]. Moreover, experiments also showed that exposure of mouse stem cells to THz radiation changed the expression of specific genes resulting in a change in cell morphology [3].

When living cells are exposed to high-power THz, an appreciable amount of energy is deposited on the surface of these molecules. Therefore, THz-induced bioeffects are believed to be primarily mediated by the temperature rise generated during exposure (i.e., hyperthermal effects). However, given that THz radiation can strongly interact with water and macromolecules, whose lifetime scales are on the order of a picosecond, it has also long been argued that THz radiation can exert its effects through coherent excitations and/or nonlinear resonance mechanisms [1]. The question of whether cells exposed to high-power THz radiation exhibited comparable responses as those of conventional hyperthermia still remains unanswered. In this study, we compared the global effect of a continuous-wave, single-frequency, 2.52 THz and a thermally-matched, bulk-heating (BH) on the expression of mRNAs and microRNAs (miRNAs). Full gene expression profiling was performed using microarray GeneChips® (Asuragen Services, Austin, TX) and evaluated using bioinformatics analysis tools.

II. RESULTS

In our initial set of experiments, we sought to determine the temperature rise that would be generated in cells exposed to 2.52 THz radiation (υ = 2.52 THz, Φ = 636 mWcm^{-2}) for 40 min duration. Our computational and empirical dosimetric data showed that the temperature increased 6 °C during exposure. We then used this value to set the thermally-matched BH protocol at 44 °C for 40 min.

To get a comprehensive view of the transcriptional response to THz irradiation, we exposed Jurkat cells to 2.52 THz frequency or BH and used microarray GeneChips® to examine mRNA and miRNAs expression changes in each exposure condition versus sham (unexposed cells). For interpretation of data, we employed the Ingenuity Pathways Analysis tool (IPA, version 8.7, Ingenuity® Systems Inc., Redwood City, CA) as well as other web-based resources such as the GeneCards Human Gene Database and The HUGO Gene Nomenclature Committee.

In Fig. 1, we display the total number of significantly differentially expressed mRNA and miRNAs transcripts that we identified in THz- and BH-exposed cells.

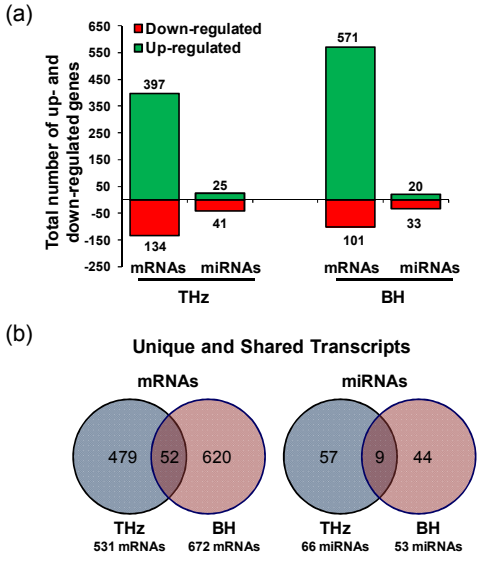

Fig. 1. The total number of differentially expressed mRNAs and miRNAs in THz- and BH-exposed cells. Biomarker comparison analyses were performed using IPA. mRNAs were filtered for a fold change value ≥ 4 and a p-value ≤ 0.05. The significant cutoffs for miRNAs were set at a fold change value ≥ 1.5 and a p-value ≤ 0.05.

The data show that 531 and 672 mRNAs were significantly differentially expressed in THz irradiation and BH,

respectively. For miRNAs, we found that the expression of 66 and 53 miRNAs was significantly altered by THz and BH exposures, respectively. To determine whether any of the differentially expressed mRNAs and miRNAs was common in both THz and BH-exposed cells, we performed a biomarker comparison analysis using IPA. This tool allowed us to separate the identified mRNAs and miRNAs into three groups: unique to THz, unique to BH, and shared between THz radiation and BH, as shown in the Venn diagram of Fig. 1(b). These results showed that THz and BH shared only less than 10% and 17% mRNAs and miRNAs transcripts from the total differentially expressed mRNAs and miRNAs transcripts, respectively. The significant difference in THz and BH differentially expressed transcripts suggested that the intracellular signaling pathways triggered in either THz or BH might potentially be different.

We next sought to determine the signaling pathways that were affected in cells in response to THz and BH. Using IPA, we scored 211 and 155 signaling pathways in THz and BH exposure, respectively. Next, after setting the threshold cutoff of all signaling pathways at p-value ≤ 0.05, we scored 18 significant signaling pathways in THz radiation exposure [Fig. 2(a)] and 13 significant signaling pathways in BH exposure [Fig. 2(b)]. Surprisingly, we found that all these significantly identified signaling pathways were unique to either THz or BH exposure.

Next, in order to get a clear picture of the roles of all the identified signaling pathways, we sorted them by their respective categories. We found that although the signaling pathways were specific to the type of exposure, most belong to four pathway categories that are present in both THz and BH. These pathway categories are Cellular Growth Proliferation and Development, Intracellular and Second Messenger, Organismal Growth and Development, Cellular Immune Response and Nervous System, as shown in Fig. 2(a) and Fig. 2(b). The signaling pathway categories that were exclusive to either THz radiation or BH exposure included Growth Factor, Cell Cycle Regulation and Disease-specific signaling pathways in THz radiation exposure, and Cardiovascular, Cytokine and Nuclear receptor signaling pathways in BH exposure.

III. Summary

In this study, we showed that both 2.52 THz irradiation and BH induce a significant change in the expression of many mRNA and miRNAs. However, most of the differentially expressed transcripts were unique to either exposure type. Furthermore, we showed that the signaling pathways significantly scored were unique to THz radiation or BH. In conclusion, the results showed that 2.52 THz frequency triggers specific signaling pathways that were not observed in BH and thus they suggest that THz radiation might elicit distinct biochemical and cellular responses than those stimulated by conventional hyperthermia.

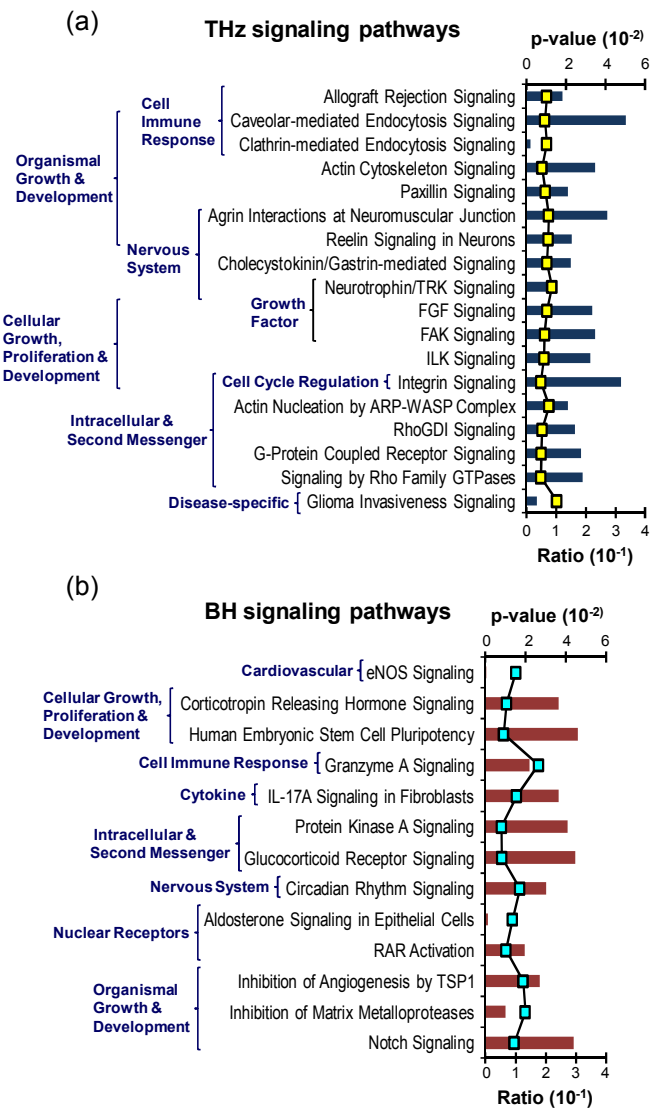

Fig. 2. THz radiation and BH scored signaling pathways. (a) Significant signaling pathways scored for THz radiation exposure. (b) Significant signaling pathways scored for BH exposure. The signaling pathways significance cutoff was set at p-value ≤ 0.05. The p-value is calculated based on the proportion of significant genes that map each particular pathway. The ratio plot indicates the number of the significant genes expressed in the data relative to the total number of genes in that particular signaling pathway.

Acknowledgments

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