REVIEW

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HUMAN CELLS RESPONSE TO ELECTROMAGNETIC WAVES OF RADIO AND MICROWAVE FREQUENCIES

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Human cells both generate and absorb electromagnetic waves (EMW), but information about sensing and responding to EMW at different Hz frequencies is still fragmentary. The reported impact of radio (RF) and microwave (MW) frequencies is variable, from harmful to human health to applications promising for novel diagnostics and treatment of diseases, e.g., cancer. The review highlights both recent achievements in elucidation of molecular mechanisms of RF and MW effects and a direction for their successful practical application in humans.

K e y w o r d s: electromagnetic waves, radio frequency, microwaves, human cells, molecular mechanisms, diagnostics, treatment.

There is no doubt that the non-ionizing and non-thermal application of electromagnetic waves (EMW) with radio (RF) and microwave (MW) frequencies affect human health. The harmful impact of EMW is reported for the radiation from mobile phones, transmission stations, radars, and power lines. [1] The positive impact of EMW on human health is also reported (Fig. 1). This review attempts to map studies of non-thermal RF and MW radiation impact on human physiology. This type of radiation holds promises of specific modulation of regulatory processes. Technical and biomedical challenges in studying emission and reception of RF and MW EMW by humans severely limit transformation of promises into clinical applications. Here, we highlight recent achievements, challenges, and directions for a successful practical application of RF and MW studies in humans.

1. Human cells and tissues generate EMW

Cells, tissues and organs of the human body generate electromagnetic waves. The diagnostic importance of the components of electromagnetic fields, i.e., electric currents and magnetic field, is confirmed by electrocardiography (ECG), electroencephalography (EEG), and magnetoencephalography (MEG). However, studies of EMW emission in RF and MW frequencies are limited (Fig. 2). Technical challenges, including measuring weak fields, frequencies, waveform and modulation of human EMW, are the possible reasons for this limitation. Fig. 1 shows the distribution of the studies of human emission of EMW. The focus is on RF and MW frequencies. The regions are of extremely low frequency (ELF) from 0.5 to 30 Hz and the region from 1.0 Hz to 150 kHz [2-5]. The other regions of detected emission by humans are infrared (IR), visible, and ultraviolet (UV) range [6-9].

There are reports that the human body and human brain emit extremely low frequency EMW [2, 3]. Lipkova and Cechak reported emission of EMW at 2, 3, 4.2, 16.8, and 23.3 Hz frequencies [2]. EMW emission by a person was measured in a specially constructed chamber. The measured range was from 0.5 to 30 Hz. The magnitude of 10 to 100 times elevation of the spectral peaks above the background was defined for detection of peaks. Neither strength of the emission, nor the biomedical value of the detected emission was reported. Despite methodological shortcomings, this study reported frequencies at which the whole body emits ELF EMW [2].

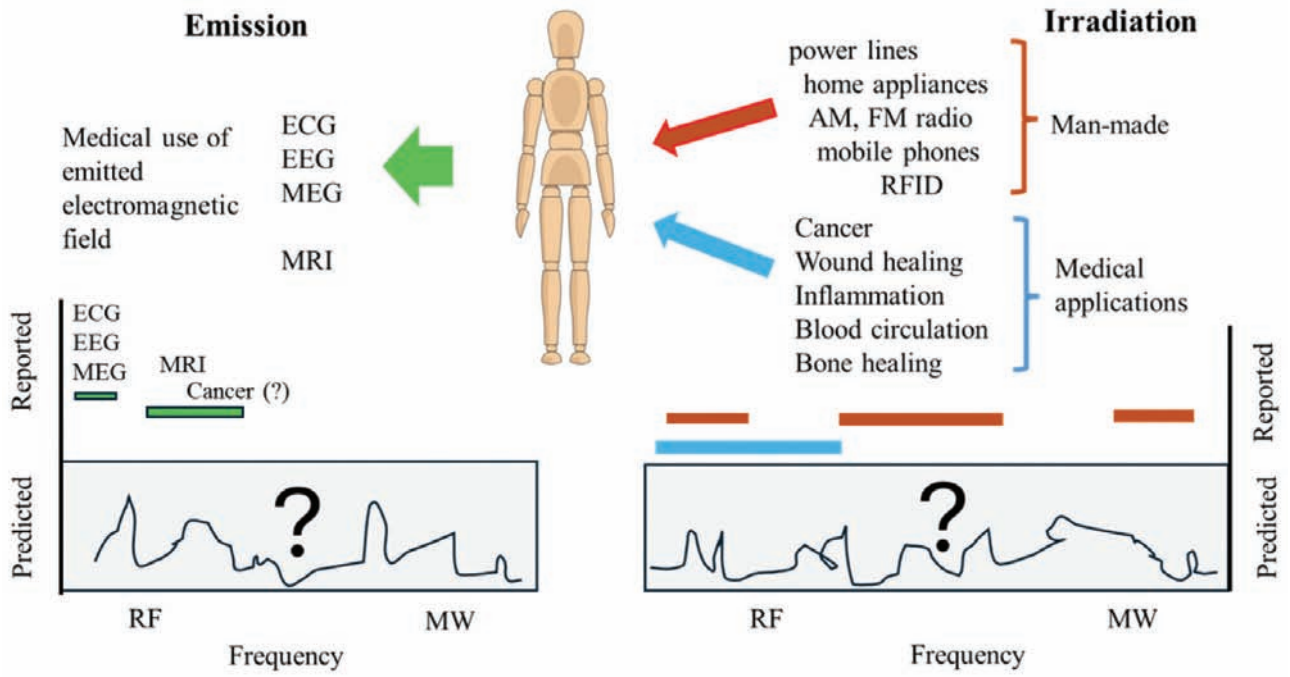

Fig. 1. Importance of the knowledge about emission and sensing of electromagnetic waves by humans. Medical use of the knowledge about the electromagnetic field emitted by humans is illustrated in the left part of the figure. EEG, ECG, MEG and MRI are examples of the use of the human electromagnetic field for diagnostics. The knowledge about man-made radiation and medical applications of irradiation of humans is illustrated in the right part. Mobile phones, RFID, radio communication, home appliances, and power lines are examples of the man-made radiation. Applications of electromagnetic fields for the improvement of healing, control of inflammation, and treatment of cancer are examples of the medical use of EMW irradiation. The lanes in the lower section of the figure illustrate the ranges of EMW used for medical applications. The color of lanes corresponds to the color annotation of emitted or absorbed EMW. Emission of EMW is annotated in green, man-made radiation in light-brown, and medical applications in blue. Question marks and grey boxes of predicted applicability indicate the "black box" of RF and MW frequencies that are not yet studied for medical purposes, despite predictions of medical applicability. Predictions are based on the biochemical and biophysical properties of the human body, its organs and cells

The human brain has a high level of electromagnetic fields, due to neural transmission. Brazdzionis et al. reported that the human brain emits EMW in the frequency range of 1 to 10 Hz [3]. The studied range covers frequencies of alpha, theta, and delta brain waves. An important observation was that the emitted radiation was detected at the distance of 63 cm. The authors reported complex spectra that were also person-dependent and varied depending on the tasks given to the person. Multiple peaks at several frequencies were recorded. However, no specific frequencies were claimed in the report. The conclusion was that the human brain emits ELF EMW that is dependent on an individual and individual's activities [3].

The efforts to identify cancer-specific frequencies of EMW emitted by cancer patients generated many profiles [4, 5]. These profiles are claimed to be specific to the type of cancer and have personalized features. Barbault et al. reported the detection of 1524 different frequencies for EMW that were claimed to be cancer-specific [4]. The frequency range of these EMW was from low Hz to 150 kHz. These claimed cancer- and patient-specific EMW were used with the carrying wave of 27.12 MHz [4, 5]. The malignancies were brain, pancreatic, ovarian, lung, thyroid, breast, colorectal, prostate, renal, and bladder cancers, neuroendocrine tumors, hepatocellular carcinoma, hematological malignancies, and leiomyosarcoma. The authors claimed that

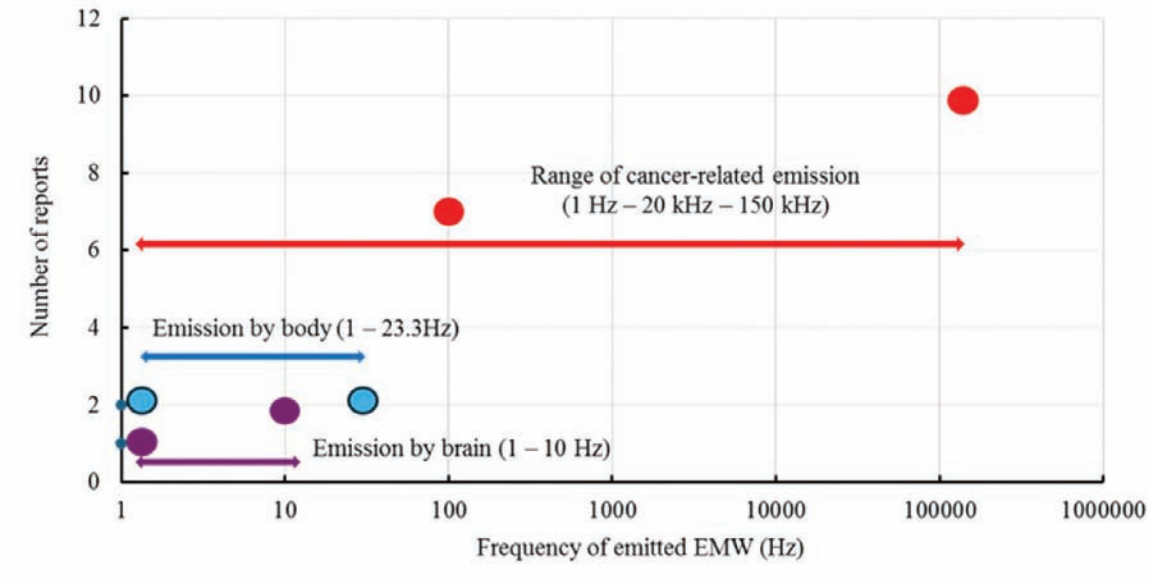

Fig. 2. Profiling of human EMW emission in the range from 1.0 Hz to 1.0 MHz. The frequency range of EMW emission by a human body, by a human brain, and by cancer patients are indicated. Dots indicate reported frequency (X axis) and number of studies (Y axis). Colors indicate studies of body emission (blue), brain emission (violet), and radiation detected from cancer patients (red). The studies which provided technical details about detected EMW are included

1873.477, 2221.323, 6350.333 and 10456.383 Hz are common frequencies for patients with breast, prostate and pancreatic cancers, and hepatocellular carcinoma. Significant variability of spectra was observed between patients and types of cancer. Clinical studies indicated that the claimed cancer-specific frequencies may indeed be used for diagnostics and treatment of cancer [5]. However, these claims require further evaluation and study. In the context of this review, the claims of tumor-specific frequencies of EMW radiation show that the humans emit EMW in the Hz – kHz range (Fig. 2).

This review does not focus on IR, visible, and UV range of EMW emission. There are many good reports about IR emission by humans, which show variations of emitted IR frequencies and intensities for different conditions, organs, and even human cells, e.g., active nerves emitting at 149 THz and 6 μW/cm^2 [6]. The development of methodology for measuring the emission of ultra-weak photons boosted studies of the visible spectra [7, 8]. Measuring ultra-weak photons emitted by humans may lead to novel diagnostics. For example, skin damage can be monitored by emission of ultraweak photons at the peak of 545 THz [7, 8]. UV EMW attracted attention as a channel of non-contact communication between cells. Scholkmann et al. reviewed data about non-contact and non-chemical communication between human cells. They claim that this communication involves UV light at a frequency above 750 THz [9].

Medical diagnostics has examples of the clinical use of human electromagnetic fields. The main emphasis is on measuring electrical currents (electrocardiography (ECG), electroencephalography (EEG)), magnetic field (magnetoencephalography (MEG)), or provoked emission of RF (magnetic resonance imaging, MRI) or microwaves (microwave imaging). These well-established medical practices confirm that the human body generates electric current and magnetic fields, which is indirect confirmation of generation of EMW (Fig. 1). However, these techniques do not describe profiles of EMW emission by humans.

Published data support the statement that humans emit EMW in practically all ranges from ELF-RF to UV, from Hz to PHz frequencies. However, profiling studies of the emitted EMW are limited and focused on relatively narrow windows of the RF frequencies (Fig. 2). This narrowness does not cover a significant diversity in combinations of frequencies, amplitudes and modulation of EMW. The introduction of a comprehensive OMICs-like analysis of EMW profiles is required for better understanding and practical application of EMW emission by humans.

2. Humans sense and react to EMW radiation

Humans sense, absorb, and react to EMW radiation. The information about sensing and response to EMW is still fragmentary. Fragmentation is due to the narrow ranges of studied frequencies, amplitudes, waveforms, experimental designs, and variability of the studied models. The most studied are EMW of frequencies used in mobile phone communication, WiFi networks, transmission towers, radars, and power lines. The main reason is health concerns due to exposure to this EMW radiation [1]. Other frequencies are studied much less. Recent interest in the study of EMW is promoted by reports of the EMW role in diagnostic and treatment of diseases, e.g., cancer (Fig. 3).

The response to EMW depends on the type of EMW and the biological mechanisms involved in sensing of the radiation. The impact of EMW exposure varies for different species due to species-specific absorption, resonance, interference, diffraction and distribution of EMW, e.g., in humans vs mice vs insects. For a review of the EMW impact on non-humans or thermal applications, readers are advised to dedicated publications. In this review, we present selected reports about RF and MW non-thermal action on humans and human cells.

2.1. Response to EMW of Hz frequencies

The impact of the frequency EMW of Hz bandwidth was reported on the level of sensing by individuals, the level of cell physiology, and the level of enzymatic activity.

Studies of human cancer cell lines showed that the EMW of Hz frequencies affect cell proliferation, death, and migration. A promising observation of selectivity between tumorigenic vs non-tumorigenic cells was reported by Crocetti et al. [10]. The authors reported growth inhibition of human breast cancer cells MCF-7 and no impact on non-tumorigenic

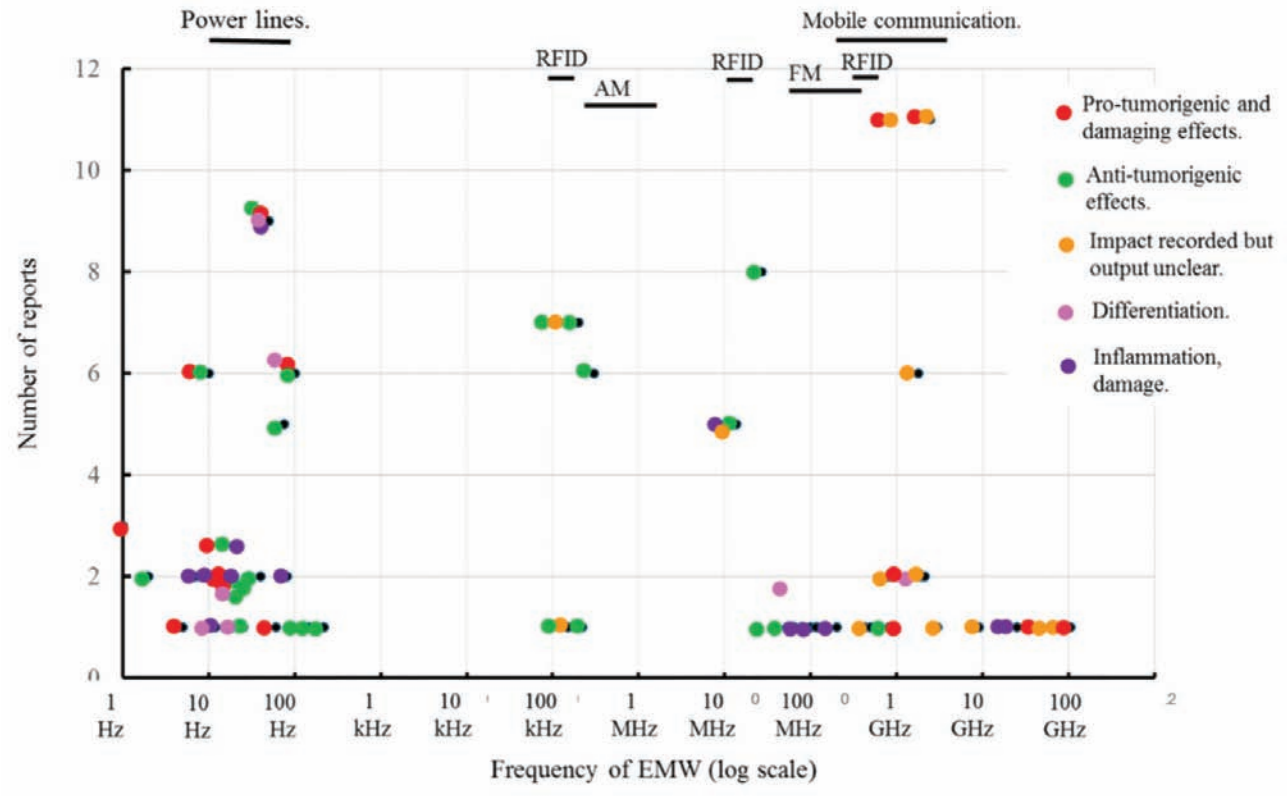

Fig. 3. Response of humans or human cells to EMW radiation in the range from 1.0 Hz to 100 GHz. Dots indicate reported frequency (X axis) and number of studies (Y axis). The predominant output of the irradiation is indicated and color coded, as indicated in the figure. The frequency ranges of different man-made emission are indicated by black lines on the top of the figure (power lines, mobile communication, AM and FM broadcasting, radio frequency identification (RFID). Note predominantly damaging and pro-tumorigenic output of the high frequency radiation, and variable outputs of the middle and low frequency radiation

MCF-10A cells after exposure to EMW of 20 Hz to 50 Hz at 2 to 5 mT for 30 to 90 min per day for 3 days [10]. This report indicated a selective impact on cancer cells vs no effect on non-tumorigenic cells. The growth inhibitory impact of 25 Hz radiation, modulated at 6 Hz, at 2 μT and 1 h per day, was reported by Buckner et al. [11]. Tested B16BL6, MDA-MB-231, MCF-7, HeLa, HBL-100, and HEK293 cells showed inhibition of growth up to 17%. The proposed mechanism includes deregulation of Ca^{2+} flux [11]. A selective impact of the EMW radiation was reported for T47D breast cancer cells [12]. The exposure of these cells to 100 Hz or 217 Hz at 0.1 mT for 24 to 72 h resulted in inhibition of cell growth without observation of cell apoptosis. Rearrangements of the cytoskeleton and enhanced production of reactive oxygen species (ROS) were observed in T47D cells [12]. Franco-Obregon reviewed findings that support involvement of Ca^{2+} and ROS generation in the cell proliferation inhibitory effect of EMW of 30 to 60 Hz at 2.5 μT [13].

An enhancement of doxorubicin efficacy in breast cancer MCF-7 cells was observed upon EMW radiation of the cells [14]. Sukumar et al. showed that pulsed at 20 x 150 microsecond pulses of 15 Hz increased doxorubicin efficacy by 30% compared to doxorubicin only. Pro-apoptotic effect of a combined application of temozolomide and EMW radiation of 75 Hz at 2 mT for 1 h every 2 days for 6 days was reported for human glioblastoma cells T98G [15]. 75 Hz radiation at 3.0 mT and pulses of 1.3 ms cooperated with A2a adenosine receptor in the inhibition of growth of human glioblastoma multiforme U87MG cells and pheochromocytoma PC-12 cells [16]. Exposure of human pluripotent embryonal carcinoma (NT2) cells to radiation with frequencies ranging from 0.01 Hz to 1 kHz at 10 nT and 15 mT induced differentiation and reduced the tumorigenicity of NT2 cells [17]. Frequency-related specificity of cellular response was observed by Akbarnejad et al. for U87 cells [18]. The authors observed variable responses to 10, 50, and 100 Hz applied at 5 mT or 10 mT, with inhibition at 10 and 100 Hz but enhancement of U87 cells proliferation at 50 Hz, 10 mT [18]. The variable response in expression of various regulators was observed for clear cell renal carcinoma under exposure to 50 Hz, 4.5 mT, for 30 min daily for 5 days [19]. Three renal carcinoma cell lines (786-O, 769-P, and CAKI-1) and a non-tumorigenic HEK293 cell line were studied. The variability in expression of different regulators indicated that the EMW triggered different molecular mechanisms in different cells. These reports show that EMW of the low frequency of Hz to kHz affects the growth of tumor cells. The mechanisms of the EMW action are poorly studied. These reports suggest also a non-linear response vs frequency. These reports are strong indicators that the low-frequency EMW has a potential for the treatment of cancer.

Human neuroblastoma SH-SY5Y cells are frequently used in neurodegeneration and neurodifferentiation studies. Published studies of these cells showed that EMW radiation at 50 or 75 Hz promoted neurodegeneration, including mimicking Alzheimer's disease. The mechanisms included an increase in antioxidant levels in injured microglia and neuronal cells, mimicking *in vitro* Alzheimer's disease upon exposure to 75 Hz 1.3 millisecond pulses [20]. Exposure to 50 Hz radiation at 1.0 mT for 24 h enhanced levels of NO and O_2 radicals, that leads to neurodegeneration [21]. These publications suggest that EMW at frequencies used in home electric grids can have an impact on neurodegeneration, if the strength of the field reaches a certain threshold. WHO recommendations concluded that the EMW of 16 Hz and in the range of 300 Hz to 300 GHz, with the absorption rate at a target of 1 W/kg or higher, modulates Ca^{2+} interaction with nerve cells in brain hemispheres and neuroblastoma cells *in vitro* [22]. This is a relatively high power that is unlikely to be emitted by a normally functioning home electric grid. Kursawe et al. reported thresholds for sensing of electric current by humans. The thresholds of sensing were defined for AC of 25-300 Hz at 5 kV/m electric field strength, and for DC of 1-8 Hz at 20 kV/m [23]. The sensing threshold for high-voltage DC transmission lines was reported at 50 kV/m [24]. Flickering or induction of phosphenes in humans was observed under exposure to 20 Hz at 8 mT, which is another support for the biological impact of low-frequency EMW on the level of the whole body [25].

Differentiation of human cells is affected by the low-frequency EMW. Lisi et al. observed that human epithelial cells changed morphology after exposure to EMW at 7 Hz, 100 μT, and of sinusoidal waveform [26]. Exposure of human pluripotent embryonal carcinoma NT2 cells to fields with frequencies of 0.01 Hz to 1 kHz at 10 nT and 15 mT induced differentiation and reduced the tumorigenicity of NT2 cells [17]. Human keratinocytes HaCaT cells were treated 1 h twice a day for 3 days, and a promotion of differentiation was observed [26]. Similar promotion

of differentiation of human oral keratinocytes exposed to EMW of 50 Hz at 2 mT was reported by the same laboratory [27]. The rearrangement of the cytoskeleton and regulatory processes correlated with the observed promotion of differentiation [26, 27].

Maturation of human dermal fibroblasts into myofibroblasts significantly increased in cells exposed to 10-12 or to 100 Hz pulsed electromagnetic fields. Promotion of cytoskeletal actin organization correlated with the promotion of maturation. Exposure to these EMW was proposed for improvement of wound healing [28]. Pulsed EMW of 40 to 80 Hz at magnetic flux density of 20 Gs (2 mT), applied for up to 2 days to HUVEC cells, accelerated angiogenesis [29]. The mechanisms included reprogramming of metabolism [29]. Differentiation-promoting effects of low-frequency EMW were also observed for mouse cells. The example is enhanced differentiation and proliferation of osteoblast cell's MC3T3-E1, exposed to 15 Hz at 0.6 mT 5 ms bursts for 15 days. An increase in NO synthesis is claimed as the mechanism [30]. Another example is inhibition of melanoma cell B16F10 growth by exposure to 7.8 Hz for 24 and 48 hours and subsequent inhibition of voltage-gated L- and T-type Ca^{2+} channels [31].

Radiation at 50 Hz and 75 Hz was found to influence stem cells differentiation and proliferation [32, 33]. Cai et al. reported delayed senescence of bone marrow mesenchymal stem cells after exposure to EMW of 50 Hz at 0.4 mT [32]. Induction of chondrogenic differentiation of bone marrow mesenchymal stem cells and chondroprotective effects of EMW radiation of 75 Hz at 1.6 to 3.0 mT were reported by Song et al. [33]. The mechanisms of this effect involved modulation of sFRP3 and Wnt/β-catenin signaling [33].

The application of extremely low-frequency electromagnetic fields is proposed for the enhancement of regeneration, wound healing, and pain management. Irradiation at 5 to 32 Hz and at 50 Hz frequencies effectively modulated inflammation, proteases activity, matrix rearrangement, neoangiogenesis, senescence, stem cell proliferation, and epithelialization in wound healing [34]. Pulsed EMW at 75 Hz and pulses of 1.3 ms at 2.0 mT stimulated deposition of extracellular matrix proteins in osteoblasts, which is associated with bone healing [35]. The same frequencies of EMW increased the number of white blood cells (WBCs) and lymphocytes but decreased the mean platelet volume (MPV) levels in exposed workers [36]. Reduction of inflammation was reported for treatments with 10 to 50 Hz [37], and for exposure to a combination of 20 to 40 Hz with 100 to 1000 Hz [38]. Trentini et al. reported that the exposure to 10 to 50 Hz at 0.05 to 0.5 mT reduced the inflammatory activity of macrophages and enhanced bone regeneration [37]. Siwak et al. reported the number of genes affected by a combination of pulsed electromagnetic fields of 100 to 1000 Hz, and low-power ultrasound therapy (20 to 40 Hz) in human primary Schwann cells [38]. These genes are involved in neurotrophin signaling, inflammation, and regeneration, and provide mechanisms for promotion of Schwann cell proliferation, reduction of inflammation, and improvement of the regenerative environment [38]. Wound healing promotion by pulsed electromagnetic fields of 80 Hz at 4 mT was also reported for mouse fibroblasts L929. EMW radiation promoted cell migration and viability [39]. Thus, the published reports show that the ELF-EMW hold promises of an efficient treatment of wound healing, regeneration, and inflammation.

The mechanisms of action of extremely low-frequency EMW may include direct, specific and selective impact on enzymatic reactions. An enhancement of laccase activity by exposure to 10, 40, and 50 Hz at 15–18 mT EMW via non-thermal influence was reported [40]. The enzymatic activity of horse radish peroxidase was studied under exposure to 130, 150 Hz [41], and 50 and 100 Hz [42]. Portaccio et al. observed an enhancement of the catalytic activity during exposure at selected frequencies 130 and 150 Hz and magnetic field strength 1 mT, and no effect at 50 Hz or at frequencies higher than 250 Hz [41]. However, another group reported that the exposure to 50 Hz at magnetic field strength of 2.7 mT inhibited the activity. The inhibition was also observed at 100 Hz and strength of 5.5 mT [42]. An inhibition of membrane-associated enzymes was observed at 2.5 mT at 75 Hz, with the threshold at 73 to 151 μT and inhibition by 54% to 61% for different enzymes [43]. Calcium-ATPase, sodium potassium ATPase, succinate dehydrogenase, photoreceptor phosphodiesterase 6, alkaline phosphatase, acetylcholinesterase, and phosphoglycerate kinase were studied. The role of enzyme embedment in the membrane was highlighted for the inhibitory effect of EMW radiation [43]. Mitochondrial electron transport chain is essential for energy production in cells. Teranishi et al. reported that the exposure to 1 to 8 Hz radiation at 10 μT 4 ms pulses for 6 weeks suppressed the mitochondrial electron transport chain in mice [44].

Considering the importance of electron transport chain for cell biology, a similar study with human cells is required. The studies with enzymes are a strong indication that the low-frequency EMW may act by modulating catalytic activity of enzymes.

Fig. 3 shows that the efforts in studying the low frequencies of EMW are focused mostly on frequencies used in electric engineering and power transmission. Variability in responses related to cancer, differentiation, regeneration and inflammation were reported. These variations highlight that this range of frequencies affects humans, and that the mechanisms of the variability must be studied to ensure efficient clinical applications of EMW.

2.2. Response to EMW of kHz and MHz frequencies

The bandwidth of kHz and MHz includes frequencies used in radiocommunication, e.g., long and medium waves AM broadcasting. These frequencies are also used in radiofrequency ablation (RFA; 350–500 kHz) and magnetic resonance imaging (MRI; 1.0–100 MHz). The ability to cause lesions, like thermal lesions in RFA, promoted studies of this bandwidth for cancer management by non-thermal regulatory activities. Fig. 3 shows a distribution of studies vs frequencies and indicates impacts on humans and human cells.

Wu et al. reported that the radiation at 100, 150, 180, 200, or 220 kHz for 24, 48, or 72 h at the electric field strengths of 1.0, 1.5, or 2.2 V/cm, inhibited proliferation of U251 glioma cells and primary cell cultures prepared from 20 glioblastoma patients [45]. It must be noted that the field strength of 2.2 V/cm (220 V/m) is significantly higher compared to the safety limit for low-frequency EMW radiation at the electric field strength 0.06 V/cm (6 V/m). Therefore, the high field strength may cause non-specific damage to cells.

A strong inhibition of cell growth by 60% was reported for human breast cancer MCF-7 cells after exposure to 53.57–78.33 MHz at a power density below 0.001 mW/cm^2 [46]. This power density is close to the safety limit of 0.0009 mW/cm^2.

There were many reports about the use of EMW radiation at 100 to 300 kHz for the treatment of cancer patients. This modus of EMW application is called Tumor Treating Fields. Kirston et al. reported an inhibitory effect of alternating electric fields on cell proliferation [47]. Cells of different origins were studied, i.e., glioma, glioblastoma (U-118, U-87, F-98, C-6, RG-2 cell lines), non-small cell lung cancer (H-1299), breast cancer (MDA231), prostatic adenocarcinoma (PC3), melanoma (B16F1), and colon carcinoma (CT-26). The cells were exposed to 100 to 300 kHz for 24 h at the electric field strength up to 2 V/cm (or 200 V/m). This field strength is significantly higher than the safety limit of 6 V/m for low-frequency fields. The authors claimed that the mechanism includes disruption of microtubule formation [47]. The reported protocol was developed into a clinical application, and was elaborated with cultured cells, animal models, and in clinical trials. One of the examples is the study that reported an inhibitory effect of 100 kHz for B16F1 cells, 150 kHz for MDA-MB-231 cells, and 200 kHz for rat glioma F-98 [48]. Ten glioblastoma patients were treated at 200 kHz, 1-2 V/cm, and showed variable responses, from 1 full response,1 partial, 1 minimal, and recurrence and no effect for 4 patients [48]. The limited overall response is in line with the interference with the cell proliferation due to relatively high strength of the applied electric field [48]. Recent reviews by Jones et al. and Riegel et al. are examples of summaries that show that exposure of cultured cells and cancer patients to alternating electric fields at frequencies from 100 to 300 kHz at field strength higher than the safety limit, inhibited proliferation, and, subsequently, showed a limited clinical improvement [49, 50]. For example, overall survival is improved only for 4 months, and the progression-free period is prolonged by only 2.8 months for glioblastoma patients [50].

The frequency 13.56 MHz is used in radiofrequency identification devices (RFID). These devices are broadly used in access systems and for tracking of items. Repeated exposure of humans to this frequency encouraged exploration of its health effects. Induction of stress, cell death and inhibition of cell proliferation are the reported outcomes. Exposure to 13.56 MHz for 5 min induced changes in the cell morphology, adhesion, and motility of human pancreatic cancer cells AsPC-1 and Panc-1 [51]. Generation of ROS and damage to mitochondrial respiration were suggested as the mechanisms of action. [51, 52]. Induction of apoptosis of human colorectal cancer cells HT29, SW480, LoVo, SW620, and HT1116 upon exposure to 13.56 MHz was reported by Wust et al., 2022 [53]. Exposure at specific absorption rate of 40 W/kg of colorectal cancer cells HT29 and SW480 resulted in inhibition of cell proliferation. The authors suggested that the mechanism included modu-

lation of the ion flow, and generation of DC voltage of appr 1 μV in cells [54].

Efforts to identify cancer- and patient-specific frequencies were reported. The carrier wave in this study is 27.12 MHz wave. This carrier wave was modulated in the range from 100 Hz to 150 kHz [4, 5, 55-60]. Inhibition of breast, kidney and liver cancer cells was reported after exposure to the carrier wave 27.12 MHz modulated at 100 Hz to 22 kHz and specific absorption rate (SAR) 0.03–0.4 W/kg [55-57]. The study by Sharma et al. reported that this exposure suppressed the formation of brain metastasis of breast cancer [56]. Transfer of these studies to clinical trials showed limited success, and the clinical benefit still needs to be confirmed. The numbers of cancer-specific profiles range from 194 frequencies with modulation range 100 Hz to 21 kHz, and to 1524 frequencies with modulation range 0.1 Hz to 114 kHz [4, 58]. The mechanism of action is claimed to be an effect on microtubule organization, mitochondria functions and metabolism [5]. A three-fold increase in the production of nitric oxide and Ca^{2+} modulation was observed in neuronal cells MN9D exposed to 27.12 MHz radiation pulsed at 2 Hz and at 2.5 μT [59]. Upregulation of interleukin genes that may promote resolution of inflammation was observed in human dermal fibroblasts, epidermal keratinocytes and mononuclear cells exposed to 27.12 MHz signal delivered in 42 μs pulses of 1 kHz period [60]. The studies with 27.12 MHz carrier wave hold a promise of unveiling personalized and cancer type-specific frequencies. The application of frequencies that selectively block only cancer cells may deliver an efficient treatment.

The 800–950 MHz bandwidth is used in radiocommunication and in the Global System for Mobile (GSM) Communication. The use of mobile phones raised concerns about the safety of GSM electromagnetic fields. The primary targets for studies were the brain, brain cells, and brain malignant cells. The results varied from no effect and to alarming observations. Studies of human neuroblastoma cells SH-SY5Y reported growth inhibitory and enhanced apoptosis effects [61], or no effect on growth and differentiation [62, 63], or apoptosis [64]. These studies used SAR of 1–4 W/kg and exposure for 2, 24, 48, or 72 h. The authors reported impacts on molecular signaling processes, even if no effects on proliferation, apoptosis, or differentiation were observed. For example, a transient increase in oxidative stress and autophagy markers expression was observed [64]. Impairment of mitochondrial respiration was recorded [63]. These reports indicated that the SH-SY5Y cells are sensitive to exposure at 900 MHz or 935 MHz but the output on cell proliferation, apoptosis and differentiation varies from no effect to the inhibition of growth and enhancement of apoptosis. Similar conclusions were made for human NB69 neuroblastoma, CHME5 microglial cells, and T lymphocytes exposed to 800 MHz and 900 MHz EMW. NB69 cells did not show significant changes in gene expression, while the same exposure resulted in up- or down-regulated genes in U937 lymphoblastoma and HL-60 leukemia cells [65]. The exposure to 900 MHz at 1mW input and SAR 3.5 W/kg for 2 h to 48 h reduced viability of CCRF-CEM leukemia T-lymphoblasts [66]. Lim et al. reported that mobile phone radiation is not a stressor for normal human lymphocytes and monocytes, in contrast to mild heating, at SAR up to 3.6 W/kg and 900 MHz exposure duration for 20 min to 4 h [67]. The variability of outputs in cell growth, apoptosis, and differentiation overlaps with the variability of affected molecular regulatory mechanisms, such as gene and markers expression, mitochondrial functions, Ca^{2+}/calmodulin signaling, and toxicity regulation. Gherardini et al. reviewed potential reasons for this variability and concluded that the different methodologies lead to variable results [68]. The variability of genomes and proteomes, including a phosphoproteome, is another factor contributing to the variability of responses to the GSM radiation, as it was reported for human endothelial cells EA.hy926 and EA.hy926v1 exposed to 900 MHz at 2.8 W/kg [69, 70].

Alterations in EEG were reported upon exposure of humans to 900 MHz pulsed at 14 and 217 Hz and SAR 2 W/kg. The EEG alterations varied among 30 tested individuals, suggesting individual variability of the EEG response [71]. This report by Schmid et al. is in line with studies of cultured cells that showed variability of the outputs of the 900 MHz radiation.

Chromosomal aneuploidy was studied due to concerns of mobile phone radiation impact on the embryonal development. One report showed that there was no change in the rate of aneuploidy of chromosomes 11 and 17 in human amniotic cells exposed to 900 MHz for 24 h and SAR from 0.25 to 4 W/kg [72]. Another report showed a linear increase in aneuploidy of chromosome 17 in human peripheral blood lymphocytes as a function of the SAR value [73]. The SAR values in this study were

higher than those reported by Bourthoumieu et al., and were from 1.6 to 8.8 W/kg. Irradiation frequency was 830 MHz [73]. Therefore, the most probable reason for chromosomal aneuploidy is the high intensity of mobile phone radiation.t At the levels below recommended safety limits of 4-6 W/kg, aneuploidy is not expected.

A reduction of Aβ40 and Aβ42 proteins levels was reported in human fetal brain exposed to 918 MHz at 0.2 W/kg or 64–100 MHz at 0.4, 0.6, and 0.9 W/kg [74, 75]. The mechanism of this effect may include regulation of oxidative stress, generation of ROS, mitochondrial functions, p38 MAPK and ERK1/2 signaling.

Molecular mechanisms of action of kHz to MHz radiation include also impacts on the enzymatic and single-molecule levels. Ca^{2+} flux is one of the targets of EMW radiation. Ca^{2+} flux is affected by exposure to EMW of various frequencies, including MHz waves modulated at Hz frequency. An exposure of neuroblastoma cells to radiation at 147 MHz with amplitude modulation of 80% at 16 Hz and SAR 0.05 W/kg resulted in enhanced Ca^{2+} efflux. The peaks of the Ca^{2+} efflux were at the 13-16 Hz and the 57.5-60 Hz of the modulation range [76]. An example of an impact on enzymatic reaction is the upregulation of activity of lactate dehydrogenase exposed to 500 MHz and 900 MHz radiation [77].

Detection of resonance peaks confirms that the EMW radiation affects structure and function at the level of a single molecule. Complexity of the resonance patterns is exemplified by the peaks for tubulin and microtubule. Reported resonance peaks for tubulins are 37, 46, 91, 137, 176, 281, and 430 MHz, 9, 19, 78, 160, and 224 GHz, and 28, 88, 127, and 340 THz. Microtubule resonance peaks are 120, 240, 320 kHz, 12, 20, 22, 30, 101, 113, 185, and 204 MHz, and 3, 7, 13, and 18 GHz [78]. Knowledge of resonance frequencies offers possibilities to control specifically only selected molecules. The application of resonance frequencies to induce a resonance catastrophe and control functions of the molecule was reported [79]. Müllegger et al. showed that radiofrequency tunneling at 115 MHz of single molecules of alpha-, beta-bisdiphenylene-phenylallyl induced structural changes in the molecule, with the ultimate bond breaking (resonance catastrophe) [79].

Fig. 3 summarizes the data that show predominantly cytotoxic or cytostatic effects of EMW of kHz and MHz frequencies. Some of these cytotoxic effects may be associated with the use of radiation above the safety limits for humans. Other effects can be associated with modulation of ion flux, especially Ca^{2+} flow. Despite unclearness in the mechanisms, these reports show that EMW of kHz and MHz frequencies have a potent biological activity.

2.3. Response to EMW of the GHz frequencies

The majority of studies in these frequencies are centered around frequencies used in communication, e.g., in wireless local area network (WLAN). Humans are constantly exposed to WLAN radiation. Safety concerns regarding WLAN exposure drove studies of these frequencies (Fig. 3).

Promotion of cell death was reported for human oropharyngeal epidermoid carcinoma KB cells, neuroblastoma SH-SY5Y cells, glioblastoma U118-MG and U118 cells, human colonic adenocarcinoma Caco-2 cells, and H1299 human lung cancer cells [80-88]. Caraglia et al. reported a strong 45% death of human oropharyngeal epidermoid carcinoma KB cells after 3 h exposure to 1.95 GHz at SAR 3.6 mW/kg. Upregulation of HSP90, HSP70 and HSP20 correlated with the death response [80]. Human neuroblastoma SH-SY5Y cells responded with enhanced cell death and upregulation of ROS to an exposure at 1.8 GHz at 0.23 W/kg for 3x10 min/day for 2 days [81]. Increase of SAR to 4 W/kg with shorter exposure time did not promote cell death [82]. The exposure to 1.8 GHz was pulsed with 5 min on and 10 min off, for 1, 6, and 24 h. The difference in results suggests a non-linear response to the parameters of EMW exposure, such as modulation and frequency of application.

Reduction of viability of glioblastoma cells U118-MG and U118 was reported upon exposure to 2.1 GHz at SAR 1.12 W/kg and 2.4 GHz frequencies [83, 84]. Induction of caspases CASP3, CASP8, and CASP9 after 24 h and 48 h treatment correlated with U118-MG cells apoptosis [83]. An exposure to 2.5 GHz at electric field strength 0.2898 V/cm of Caco-2 human colonic adenocarcinoma cells promoted apoptosis of the cells [85]. Enhanced apoptosis was also observed for H1299 human lung cancer cells exposed to 75–105 GHz at power density 0.2 mW/cm^2 [86]. At the same exposure conditions, no cell death was observed for breast non-tumorigenic MCF-10A cells [86]. Differences in cell viability by cells exposed to 2.45 GHz for 1 h showed variations in responses, from no effect to 48% of cell death. The authors tested the following cell lines:

HL-60, MCF-12A, MCF-7, MDA-MB-231, Panc-1, HGC-27, KATO III, and T98G. They observed that the cancer cells responded with cell death from 10% to 48%, while no significant effect was observed for non-tumorigenic MCF-12A cells [87]. Gene expression studies generated data showing an engagement of mechanisms of cell death induction. Lee et al. described expression of 221 genes after 1 h and 759 genes after 6 h exposure of HL-60 cells to 2.45 GHz. Classification of genes showed upregulation of regulators of apoptosis and downregulation of cell cycle regulators [88]. Further OMICs studies are required to explain mechanisms of the variability of responses.

Gene expression study of primary human skin cells exposed to 60.4 GHz for 1, 6, and 24 h at 1.8 mW/cm^2 and SAR 42.4 W/kg reported 130 modulated transcripts [89]. Expression of 53 genes was affected in human fibroblasts by exposure to 2.45 GHz at SAR 0.7 W/kg, despite that the authors did not observe significant changes in cell proliferation or cell death [90].

Impacts of EMW radiation at 1.8 and 2.4 GHz on the physiological processes were reported. A decrease in motility and vitality of human spermatozoa was reported after exposure to 1.8 GHz at SAR 5.0 W/kg or higher [91]. Irradiation at 2.45 GHz and SAR 1.0-2.5 W/kg also induced oxidative damage of spermatozoa [92]. Damage to human lens epithelial cells was observed after exposure to 1.8 GHz at SAR 3 W/kg. An induction of HSP70 was detected. The damage was transient, and recovery was after 1 h. The damage was assessed by the comet assay [93]. A genotoxic effect of 1.95 GHz at SAR 2.0 W/kg was described for human fibroblasts [94]. Genotoxicity was reported for human lymphocytes exposed to 1.748 GHz at SAR 5.0 W/kg [95]. The similar exposure to 1.8 GHz at 2.0 W/kg of human Mono Mac 6 cells with characteristics of mature monocytes did not induce apoptosis or necrosis [96]. A genotoxic effect of exposure to 25 GHz radiation of human fetal and adult fibroblasts was reported as an induction of aneuploidy [97]. No impact on apoptosis or cell growth was reported for embryonic neural stem cells, exposed to 1.8 GHz at 1, 2, and 4 W/kg for up to 3 days. The only recorded effect was an inhibition of neurite outgrowth of eNSC differentiated neurons after 4 W/kg exposure for 3 days [98]. The study of human T lymphocyte Jurkat-T cells showed that the exposure to 2.45 GHz at 5.0 mW/cm^2 affected cell death only in the context of additional stimuli, e.g., in the context of Fas-dependent apoptosis [99].

The responses to EMW radiation in the GHz frequencies vary from no effect, to affecting different intracellular mechanisms without detectable impact on the cells, and to observation of damage by the radiation. Fig. 3 shows that the number of studies that reported a full control of the radiation and targeted biological models is still too low.

2.4. Response to EMW of THz frequencies

THz frequency is higher than the radio and microwave range and subsequently is not the primary focus of this review. Here, THz is briefly mentioned to emphasize that the non-ionizing EMW of biological importance are also beyond RF and MW frequencies. The non-contact communication of human cells by UV radiation is the phenomenon that leads to novel channels of communication between cells [9]. Another important communication phenomenon is emission and absorbance by cells and tissues of ultra-weak photons and identification of spectra of visual, IR and UV emission by human tissues, e.g., skin [7, 8, 100]. Note that these effects are non-thermal. The third important point is that single molecules show absorption peaks in THz range. These peaks can be evaluated for modulation of functions of the molecules. Examples are the detection of peaks of absorption by 5-methyl-cytidine at 1.29, 1.74, and 2.14 THz [101], and the detection of resonance frequencies of cancer methylated DNA in 0.4 THz to 2.5 THz range [102]. These data strongly support that the non-ionizing and specific interactions with radiation of THz frequencies must be combined with studies of RF and MW frequencies.

3. Methodology of data review and analysis

PRISMA guidelines were followed in preparation of this review [103]. MeSH terms-defined literature search of MEDLINE (PubMed) and Scopus (Elsevier) was performed by the 14th of March, 2025. The search of PubMed was performed with keywords “electromagnetic waves human”, “electromagnetic field human”, “radio frequency emission human”, “microwaves frequency emission human”, “microwaves waves absorbance human” “radiofrequency human”, “microwaves human”, with numbers of hits from >3,00 to >35,000. All these publications were screened for relevance by reading abstracts at the first step. More than 300 publications were selected for reading the main text. The inclusion criteria were reporting emission or absorption of EMW of radio or microwave frequencies by humans or

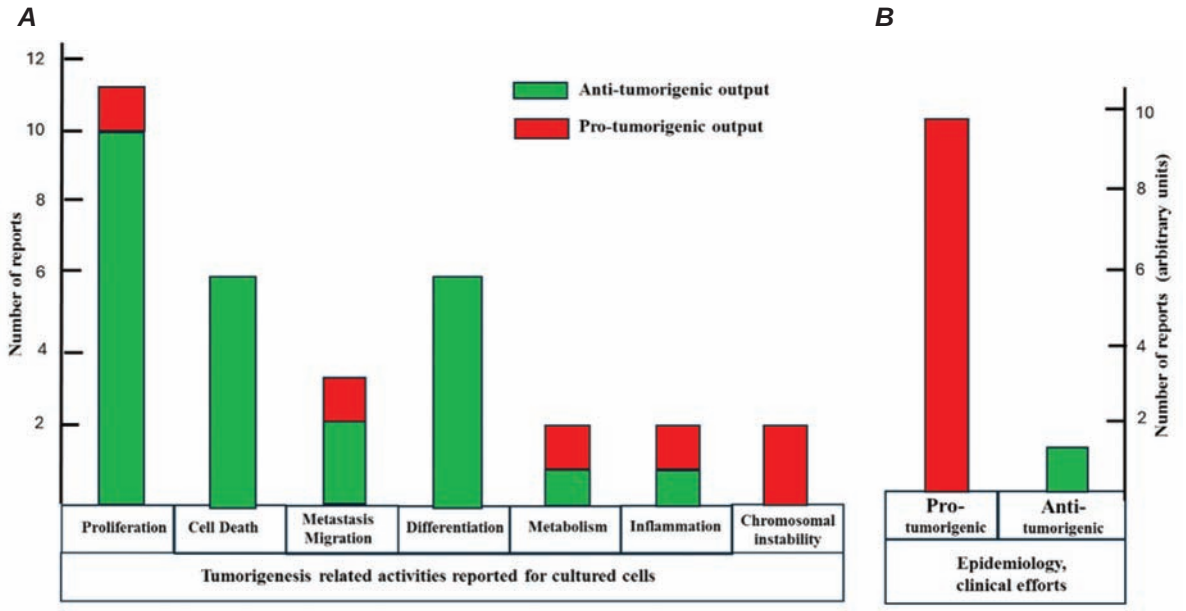

Fig. 4. Exposure to RF and MW EMW affect cancer hallmarks. ***A****) Affected cancer hallmarks are indicated for studies with cultured human cells. Outputs of the EMW action are color-coded for pro- (red) and anti- (green) tumorigenic. Predominantly, anti-tumorigenic impact on cell proliferation, death, migration, metastases, and differentiation was reported. Variable impact on metabolism and inflammation, and 2 reports of induction of chromosomal instability in cultured cells are marked. The impact of EMW radiation on other cancer hallmarks remains to be elucidated.* ***B****) Clinical observations and epidemiological studies reported predominantly pro-tumorigenic outputs. These were studies of individuals exposed to RF or MW. Note the difference in outputs of studies of cultured cells (****A****) and individuals (****B****)*

human cells. Only reports that describe specifics of electromagnetic waves/fields were considered, e.g., reports with descriptions of frequencies, amplitude, wave modulation, SAR, field strength, and control of thermal effects. Publications of thermal effects were excluded.

4. Conclusions

Accumulated knowledge shows that RF and MW electromagnetic waves are regulatory components of human physiology, despite large gaps in the knowledge (Fig. 1). These EMW are generated within the human body and by human cells, and influence regulation of normal physiological processes and diseases (Fig. 2). Humans and human cultured cells are under constant exposure to EMW of RF and MW frequencies. The concerns about an impact on health are justified by the reported observations. Exposure to RF and MW EMW may also have an impact on both triggering and treatment of diseases (Fig. 3). Cancer is an example of the variable impact of EMW on the disease progression (Fig. 4). EMW can impede tumorigenesis by acting on some cancer hallmarks, e.g., by inhibiting growth of cells, promoting cell death and differentiation, and modulation of inflammation. EMW can also promote tumorigenesis by inducing stress in cells, oxidative damage, promoting cell migration, metabolic reprogramming, and promoting chromosomal instability (Fig. 4). In most reports, the molecular mechanisms of EMW action are not explored or they are studied with a focus only on selected signaling reactions. The cancer epidemiology reports predominantly harmful effects of EMW radiation (Fig. 4). However, studies on cultured cells stimulate the use of EMW for cancer treatment. These studies show that EMW of signaling-resonance modality at the field strength below safety limits may control cancer-related mechanisms very specifically. This specificity allows elimination of only cancer cells, with no harm to normal cells, under condition that the delivered EMW energy is not harmful and is below the safety limits. Thus, the absence of off-target action of EMW minimizes side effects. To capitalize on the full potential of EMW role in human physiology and treatment of diseases, standardization of experi-

mental design is required. Translation of the findings from *in vitro* models to clinical trials is the next step in bringing EMW-based treatment to clinics.

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ВІДПОВІДЬ КЛІТИН ЛЮДИНИ НА ЕЛЕКТРОМАГНІТНІ ХВИЛІ РАДІО- ТА МІКРОХВИЛЬОВИХ ЧАСТОТ

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Клітини людини як генерують, так і поглинають електромагнітні хвилі (ЕМХ), але інформація щодо сприйняття та відповідь на дію ЕМХ із різними частотами Гц все ще є розрізненою. Дані про вплив радіочастот (РЧ) та мікрохвиль (МХ) є суперечливими: від шкідливого для здоров'я людини до перспективного застосування в новітній діагностиці та лікуванні захворювань, наприклад, раку. В огляді висвітлюються як новітні досягнення у з'ясуванні молекулярних механізмів впливу РЧ та МХ, так і напрямки їх практичного застосування у людей.

Ключові слова: електромагнітні хвилі, радіочастота, мікрохвилі, клітини людини, молекулярні механізми, діагностика, лікування.

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