Plasma Medicine, 8(2):163–175 (2018)

Electromagnetic Fields Induce Frequency-Dependent Radioprotection and Radiosensitization in *In Vitro* Cell Cultures

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ABSTRACT: The incidence of Kaposi sarcoma comorbidity in patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) is high. These patients tend to be more sensitive to ionizing radiation, making the management of their cancer with radiotherapy difficult. Hence, noninvasive methods to sensitize cancer cells and reduce therapeutic doses are needed. In this article, the effect of an electromagnetic field (EMF) of 27.125 MHz, modulated by 100- and 1000-Hz fields, on the radiosensitivity of Chinese hamster lung fibroblasts (V79) and human melanoma cells (MeWo) was evaluated using the colony-forming assay. Induced magnetic flux densities in cell cultures ranged from 0.05 to 0.25 μT. Preexposure of V79 to both modulated fields had no effect on their radiosensitivity, if irradiation followed within 2 h or at 6 h. Significant radiosensitization was observed when X-rays were administered 4 h after EMF exposure. Preexposure of MeWo to the 100-Hz–modulated field resulted in a significant radioprotection when irradiation followed within 6 h. However, treatment of these cells with the 1000-Hz–modulated field significantly potentiated the effect of X-rays. When cells were irradiated before EMF exposure, V79 cells were marginally protected by the 100-Hz–modulated field and sensitized by the 1000-Hz–modulated field. In contrast, the melanoma cells were slightly protected by the 1000-Hz–modulated field and sensitized by the 100-Hz–modulated field. Informed combination of low-medium frequency electromagnetic fields and radiotherapy might be beneficial in cancer management, especially in HIV-positive patients.

KEY WORDS: plasma-induced electromagnetic fields, Kaposi sarcoma, melanoma, radiomodulatory effects

I. INTRODUCTION

Kaposi sarcoma (KS) usually appears as tumors on the skin or on mucosal surfaces, such as the inner lining of the mouth. KS is now considered as an acquired immune deficiency syndrome (AIDS)-defining illness. Human immunodeficiency virus (HIV)-positive patients are at a greater risk of cancer than the general population due to a compromised immune system.[1] KS is ranked as the sixth and eighth most common cancer in South African males and females, respectively,[2] and can be treated with surgery, chemotherapy, radiotherapy, or biological therapy. Chemotherapy and radiotherapy can also weaken the immune system; therefore, people with HIV/AIDS may not be able to receive full courses of cancer treatment without risking severe side effects such as life-threatening

1947-5764/18/$35.00

infections. The HIV-positive subset of patients also tends to show higher normal tissue toxicity during conventional radiotherapy than their HIV-negative counterparts.

Pioneering studies more than half a century ago demonstrated that although radiosensitivity can be altered using modifying agents, a given modifying agent does not always change the sensitivity of different cell lines to radiation exposure in the same way.[3] This phenomenon has recently been observed whereby a dual inhibition of phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) was found to radiosensitize prostate and breast cancer cells, but acted as a radioprotector in normal prostate cells and mouse gut.[4–6] The main objective of radiotherapy is to kill tumor cells, or stop their proliferation, while protecting normal tissue. Due to an increase in the diagnosis of cancer there has been an increased desire to develop novel treatment modalities.

In light of the current rise in HIV infection and cancer diagnosis in HIV-positive individuals, combination therapy options may lead to a reduction in the amount of radiation delivered to a patient during treatment, thus reducing normal tissue toxicity. Reduction in radiation dose during radiotherapy is especially important for immunocompromised patients who are known to be more radiosensitive.[1] It has also been extensively reported that electromagnetic fields (EMF), such as electric, magnetic, and radiofrequency (RF) fields, in conjunction with chemotherapeutic agents can reverse the resistance of cancer cells.[7,8] These fields have been shown to inhibit disease progression and prolong patient survival with minimal or no side effects.[8–10] Other studies have also shown that extremely low-frequency magnetic fields can affect cell death processes like apoptosis.[11–13] Magnetic fields penetrate cells unattenuated and can thus interact directly with the DNA in the nucleus and other cell constituents.[14] There is overwhelming evidence supporting the opinion that exposure to magnetic fields has an effect on cellular functions, such as transcription, protein synthesis, proliferation, and differentiation. Cellular exposure to magnetic flux densities of 0.38 to 19 mT has led to increased transcription of c-*myc* and histone H2A.[15] These field-induced changes in transcription activity can significantly impact the net cellular response. While c-*myc* plays an important role in cell cycle regulation and cell death, histone H2A is central in DNA damage repair. Although apoptotic cell death has been shown to occur in WiDr cells at magnetic flux densities greater than 1.0 mT, tumor regression in nude mice bearing WiDr tumors was evident only at much higher intensities.[12] Antitumor and immune modulatory activity has also been demonstrated in a melanoma mouse model for a magnetic flux density of 0.25 T.[16] Acute exposure to flux densities below 1.0 mT does not exhibit antiproliferative activity, but results in increased levels of reactive oxygen species,[17] which may ultimately mediate cellular responses to other cytotoxic agents like chemotherapeutic drugs and ionizing radiation. Electromagnetic fields have also been used to successfully treat ailments such as wounds, bone fractures, and depression.[18,19] Electric fields with intensities ranging from 1.0 to 1.4 V/cm can alter the cell membrane structure leading to changes in the permeability of ions, such as Ca^{2+}, cause changes in the local pH and temperature, reorganize cytoskeletal components, and disrupt microtubule polymerization.[20] Exposing cells to electric fields can also cause modifications in gene expression and free radical production, which affects DNA structure and provokes

strandbreaks and other chromosomal aberrations, such as micronucleus formation.[20] In addition, electric fields can physically affect the movement and orientation of electrically charged molecular entities.

An extremely low-frequency magnetic field with a flux density of 1.0 mT has been suggested to induce immune cell activation through three different pathways, namely, the classical activation, the alternative activation, and the lectin-dependent activation pathways.[21] The classical activation pathway includes activation of inflammatory responses, destruction of extracellular matrix, and induction of apoptosis. The alternative activation pathway promotes extracellular matrix construction, cell proliferation, reduction of inflammation, and angiogenesis. The lectin-dependent activation pathway also initiates inflammation and apoptosis and inhibits cell growth in a way comparable to classical activation.[21] All the perturbations exerted by electromagnetic fields ultimately exert antiproliferative and anticancer effects by influencing cell cycle progression, the rate of cell proliferation, and apoptosis.[9,18,20]

The aforementioned therapeutic potential of electromagnetic fields, notwithstanding the application of plasma ray tubes (the so-called Rife Frequency Generator) in the treatment of cancer, largely remains a controversial issue. More than two decades ago, the American Cancer Society discouraged the use of devices, such as the Rife frequency generator, for cancer therapy because of the paucity of experimental and scientific evidence.[22] However, the concept of targeting prosurvival genes with characteristic resonant frequencies broadcast from a Rife device to induce cell death was recently demonstrated in a colon cancer cell line.[23] Also, a significant level of evidence exists for effectively targeting malignancies with cancer-specific radiofrequency electromagnetic fields.[24]

To test whether the antiproliferative and anticancer effects of frequencies broadcast from a Rife device could potentiate the cytotoxic effects of ionizing radiation, radiomodulatory effects of low- or medium-frequency electromagnetic fields were evaluated in Chinese hamster lung fibroblasts (V79 cells) and human melanoma cells (MeWo cells). The potential benefit of such a therapeutic approach to immunocompromised patients with superficial cancers is discussed.

II. MATERIALS AND METHODS

A. Cell Lines and Culture

The V79 cell line was established from the lung of a Chinese hamster and has a fibroblast-like morphology. These cells were used to represent normal tissue. The culture was obtained from Flow Laboratories (Irvine, Scotland). The human melanoma cell line (MeWo) was kindly provided by F. Zölzer and C. Streffer (University of Essen, Germany). The cells were cultivated as monolayers in 75-cm^2 flasks in minimum essential medium (MEM) supplemented with 20% fetal bovine serum (10% for V79 cells), penicillin (100 U/mL), and streptomycin (100 µg/mL) and incubated at 37°C in a humidified atmosphere (95% air, 5% CO_2). Cells were used for experiments upon reaching 80 to

90% confluence. For experiments, cell cultures were trypsinized and 200 to 500 cells seeded per 25-cm^2 tissue culture flask, and left to settle for 2 to 4 h (depending on cell line). The cells were subsequently exposed to an electromagnetic field for 30 min prior to or following irradiation at time points of 0, 0.5, 1, 2, 4, and 6 h. The final volume of culture medium in each flask was 10 mL.

B. Electromagnetic Field Generation and Exposure

Using an EMEM oscillator amplifier (EMEM Devices Rife Machine, Model No. 1-2012B, Boulder, CO), electromagnetic fields were generated by modulating a 27.125-MHz carrier wave with 100- and 1000-Hz square-waves with a peak-to-peak amplitude of 5 V. The modulating frequencies were generated using a GME frequency generator with an output impedance of 50 Ω and a duty cycle of 50% (GME Technology, Model No. SG-10, Pomona, CA). The resulting radiofrequency (RF) was then broadcast via a double bubble argon plasma ray tube (length = 25 cm; external bubble diameter = 6.7 cm). The set up for EMF exposure of cell cultures through a plasma Rife tube is illustrated in Fig. 1a. A maximum of 24 cell culture flasks could be exposed at a given time, and were stacked in groups of four, such that the outside dimensions of the volume occupied by the cell culture layers was 11 cm (width: 2 flasks breadthwise) × 18 cm (length: 2 flasks lengthwise) × 14 cm (height: 6 flasks by height). The perpendicular distances from the axis of the plasma tube to the cell culture planes were 10.0, 12.4, 14.8, 17.2, 19.6, and 22.0 cm. Each cell layer was covered with 3.5 mm (10 mL) of culture medium.

To estimate the magnetic and induced electric fields in the cell cultures, the plasma ray tube was assumed to function as an antenna that is transmitting at ~27.12 MHz. Nearfield magnetic field strengths for this frequency can vary between 0.5 A/m (magnetic flux density of 0.63 μT) and 0.8 A/m (magnetic flux density of 1.0 μT) at a radial distance of 12 cm from the antenna.[25] Therefore, by adopting the maximum magnetic flux density of 1.0 μT as the peak flux density in the plane 12 cm from the axis of the plasma tube (Fig. 1b), the magnetic flux densities in cell culture planes at 10 to 22 cm were deduced using the inverse-square law. The corresponding induced peak electric fields (V/m) were then calculated as $E_{peak} = 2h\pi fB$,[26] where B is the peak value peak magnetic flux density (T), f is the transmitted frequency (27.125×10^6 Hz), and $2h$ is the depth of the cell culture medium (0.0035 m). Thus, the estimated magnetic flux densities in the cell cultures ranged from 0.30 to 1.44 μT, and the corresponding peak electric fields were 0.09 to 0.42 V/m (Table 1). Using a conductivity (σ) of 1.5 S/m for the cell culture medium,[26] induced current densities (J) were calculated from the relation $J = \sigma E$. Estimated current densities in cell cultures ranged from 0.14 to 0.63 A/m^2 (Table 1). Because the ratio of the depth to the width (0.05 m) of the culture medium in each flask is less than 0.3, estimation of peak electric fields from the magnetic flux densities has an uncertainty of ≤ 1%.[26] For sham EMF exposure (0 Hz), the control samples were treated as described with the plasma ray tube turned off.

To test whether the radial variation in induced magnetic flux density across the cell culture layers had an impact on cell viability, the proportions of seeded cells that

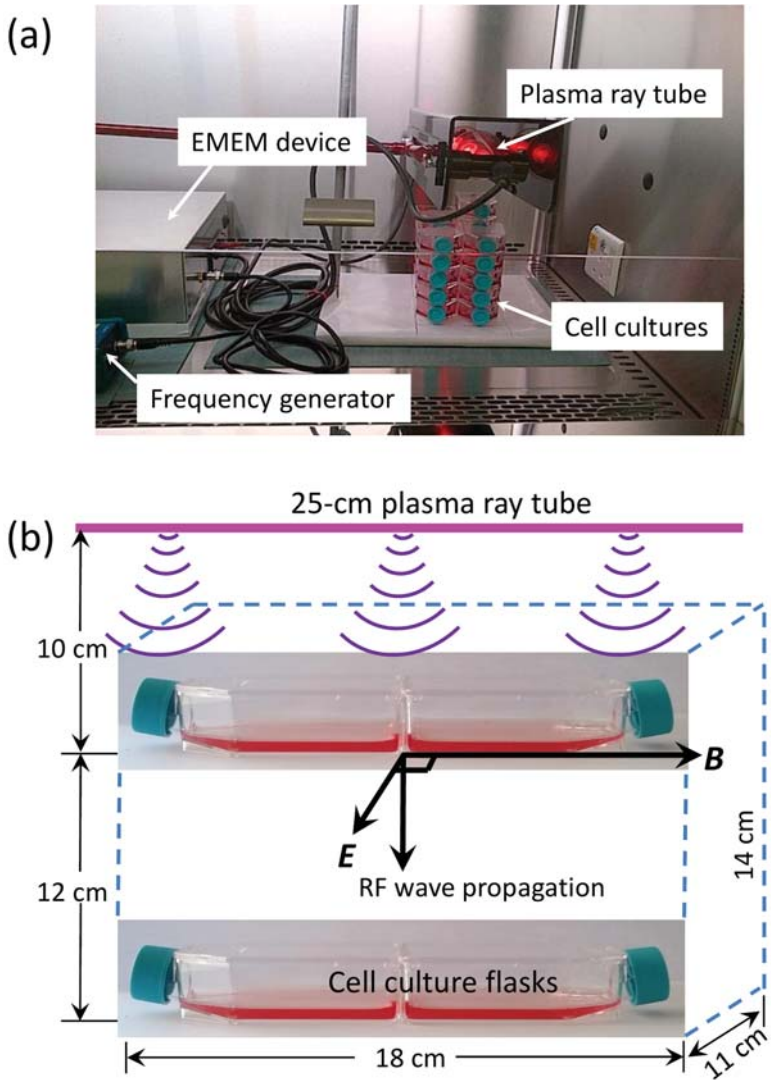

FIG. 1: (a) Photograph of the electromagnetic field (EMF) exposure system. (b) A two-dimensional schematic diagram showing the top and bottom cell culture planes of the 2 × 2 × 6 flask matrix. In the set-up, the plasma ray tube is centered horizontally above the cell culture flasks, such that the induced magnetic field (B) is parallel to the base of a flask and the induced electric field (E) in the culture medium is parallel to the width of the flask.

eventually form colonies (plating efficiencies) were determined in cell cultures placed at the different radial distances, as in Fig. 1, for 0, 100, and 1000 Hz exposures. In the current setting, no significant frequency- and location-dependent differences in plating efficiency were observed. For the V79 cells, the plating efficiency at 0 Hz (73 ± 4%) did not differ significantly from those at 100 Hz (82 ± 3%; $P = .12$) and 1000 Hz (73 ± 5%;

TABLE 1: Estimated peak magnetic flux density (*B*), electric field strength (*E*), and current density (*J*) induced at a distance (*d*) from plasma ray tube

d (cm)	B (μT)	E (V/m)	J (A/m^2)
10.0	1.44	0.42	0.63
12.4	0.94	0.28	0.42
14.8	0.66	0.20	0.30
17.2	0.49	0.15	0.23
19.2	0.39	0.12	0.18
22.0	0.30	0.09	0.14

P = .94). Similarly, the plating efficiency for sham-exposed MeWo cells (55 ± 4%) was not significantly different from those determined when the cells were exposed to 100 Hz (62 ± 7%; *P* = .30) and 1000 Hz (57 ± 6%; *P* = .82).

C. Cell Culture Irradiation, Clonogenic Cell Survival, and Radiomodulatory Effects of Induced Electromagnetic Fields

Pre-prepared monolayer cell cultures were irradiated at room temperature (20°C) at a dose rate of 1 Gy/min, using a Faxitron MultiRad 160 X-ray irradiator (Faxitron Bioptics, Tucson, AZ). Irradiation was performed at various time points relative to electromagnetic field exposure, as described above. Sham-irradiated cultures were left on the turntable of the Faxitron X-ray irradiator for 2 min with the X-ray source turned off.

The irradiated and EMF-exposed cell cultures were left in an incubator at 37°C for 7 and 14 days (for V79 and MeWo cells, respectively) for colony formation. Colonies were then fixed in glacial acetic acid:methanol:water (1:1:8, v/v/v), stained with 0.01% amido black in fixative, air-dried, and counted. Unirradiated cultures with and without electromagnetic field exposure were used as controls for EMF and X-ray treatment, respectively. Colonies containing at least 50 cells were deemed to have originated from single surviving cells and were scored. Cytotoxicity was assessed on the basis of a surviving fraction (*SF*), which was calculated from the relation: $SF = n_{col}(t)/\{[n_{col}(u)/n_{cell}(u)] \times n_{cell}(t)\}$, where $n_{col}(t)$ and $n_{col}(u)$ denote the number of colonies counted in treated and untreated samples, respectively. $n_{cell}(t)$ and $n_{cell}(u)$ are the number of cells seeded in treated and untreated cultures, respectively. Three independent experiments were performed for each time point and experimental arm. Radiosensitivity was expressed in terms of the surviving fraction at 2 Gy.

To investigate the influence of EMF exposure on radiosensitivity, the interaction between EMF and X-rays was expressed as a modifying factor (*MF*), given as the ratio of surviving fraction at 2 Gy in the absence EMF to that in the presence of EMF. The

criteria for inhibition, no effect, and enhancement of radiosensitivity by EMF are $MF < 1.0$, $MF = 1.0$, and $MF > 1.0$, respectively.

D. Statistical Analysis

Statistical analyses were performed using the GraphPad Prism (GraphPad Software, San Diego, CA) computer program. To compare two data sets, the unpaired two-sided *t*-test was used. A *P* value less than 0.05 indicates a statistically significant difference between the data sets. Data were presented as the mean (± SEM) from at least three independent experiments. For each experiment, three replicates were assessed.

III. RESULTS

Radiosensitivity was expressed in terms of the surviving fraction at 2 Gy. Figure 2 shows the relationship between radiosensitivity of the Chinese hamster lung fibroblasts (V79) and the time of X-ray treatment after EMF exposure. For time intervals ranging from 0 to 2 h, exposure to fields modulated by the 100- and 1000-Hz fields had no effect on radiosensitivity, with a modifying factor of ~0.99. Also, no effect on radiosensitivity was observed when cells were irradiated 6 h after EMF exposure (Fig. 2). However, the cells were marginally sensitized when X-irradiation occurred 4 h after EMF treatment, giving

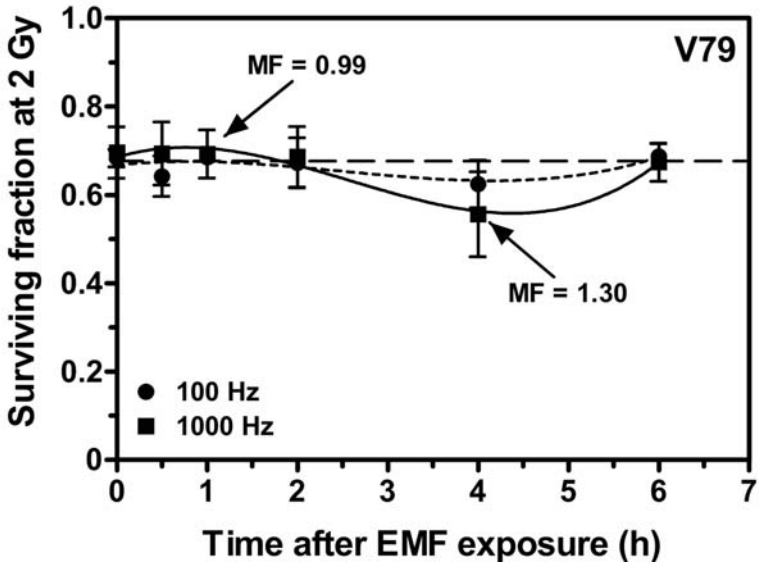

FIG. 2: Clonogenic cell survival at 2 Gy in Chinese hamster lung fibroblasts (V79), when cells were exposed to a 100- or 1000-Hz–modulated 27.125 MHz carrier electromagnetic field (EMF) prior to X-irradiation, as a function of time between EMF exposure and X-ray treatment. Data points are means ± SEM of three independent experi-ments. Horizontal dashed line represents the surviving fraction at 2 Gy without EMF exposure.

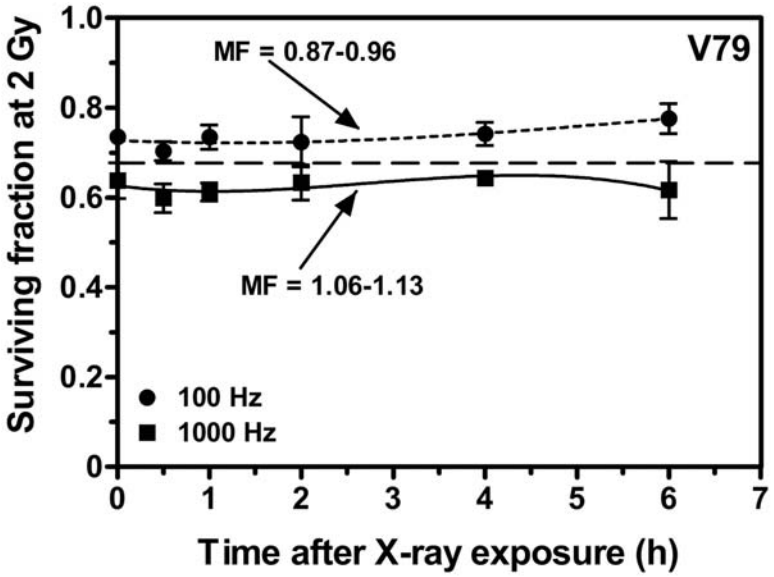

FIG. 3: Clonogenic cell survival at 2 Gy in Chinese hamster lung fibroblasts (V79), when cells were exposed to X-irradiation prior to a 100- or 1000-Hz–modulated 27.125 MHz carrier electromagnetic field (EMF), as a function of time between X-ray treatment and EMF exposure. Data points are means ± SEM of three independent experiments. Horizontal dashed line represents the surviving fraction at 2 Gy without EMF exposure.

modifying factors of 1.09 ± 0.09 and 1.30 ± 0.25 for the 100- and 1000-Hz–modulated fields, respectively.

Irradiating V79 cells to 2 Gy prior to exposure to a 100-Hz–modulated field yielded a small radioprotection, while the 1000-Hz–modulated field exposure resulted in a slight radiosensitization (Fig. 3). The corresponding modifying factors ranged from 0.87 to 0.96 and from 1.06 to 1.13, respectively. These effects were independent of the time interval between X-irradiation and EMF exposure.

Data for cell survival at 2 Gy in the human melanoma cells (MeWo), when cells were exposed to fields modulated by either the 100- or 1000-Hz–modulated field before being irradiated, are presented in Fig. 4. For all time intervals between EMF and X-ray treatment, pretreatment with the 100-Hz–modulated field resulted in significant radioprotection, with modifying factors ranging from 0.68 ± 0.04 to 0.79 ± 0.01. On the contrary, preexposure to the 1000-Hz–modulated field yielded significant radiosensitization, giving modifying factors between 1.35 ± 0.02 and 1.64 ± 0.19. The radiation modifying factors when cells were irradiated at 2 h and 4 h after EMF exposure emerged as 1.51 and 1.52, respectively (Fig. 4).

When the MeWo cells were irradiated to 2 Gy of X-rays followed by exposure to the 100 Hz-modulated field, the cells were rendered more radiosensitive, as shown in Fig. 5, with modifying factors ranging from 1.34 to 1.76. However, when X-ray

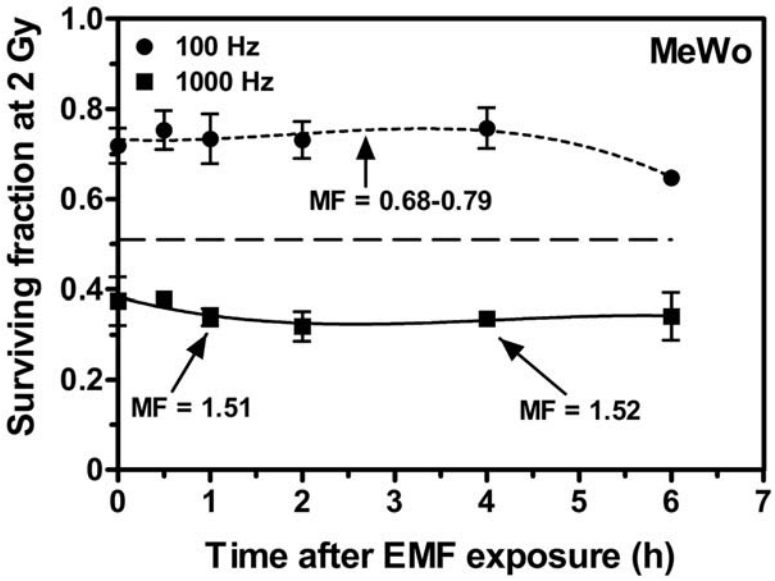

FIG. 4: Clonogenic cell survival at 2 Gy in human melanoma cells (MeWo), when cells were exposed to a 100- or 1000-Hz–modulated 27.125 MHz carrier electromagnetic field (EMF) prior to X-irradiation, as a function of time between EMF exposure and X-ray treatment. Data points are means ± SEM of three independent experiments. Horizontal dashed line represents the surviving fraction at 2 Gy without EMF exposure.

exposure was followed by treatment with the 1000-Hz–modulated field, the cells were less radiosensitive with modifying factors ranging from 0.90 to 0.94.

IV. DISCUSSION

Electromagnetic fields are known to affect the normal functioning of cells and their effects differ depending on the cell type. In this investigation, the Chinese hamster lung fibroblasts (V79) were used to represent normal tissue, while the human melanoma cells (MeWo) represented tumor cells. The current data suggest that normal tissue and cancerous cells do not respond to all electromagnetic fields in the same way. While preexposure of the V79 cells to both 100- and 1000-Hz–modulated fields followed by 2 Gy of X-rays had no effect when cells were irradiated within 2 h of EMF exposure, significant radioprotection and radiosensitization were seen in the MeWo cells for the 100- and 1000-Hz–modulated fields over all time points investigated (Figs. 2 and 4). The findings that the fibroblasts were protected by the 1000 Hz-modulated field exposure when cells were irradiated 1 h after EMF exposure and that both fields were radiosensitizing at an interval of 4 h, suggest that modulation of a 27.125 MHz carrier field with a 1000 Hz field may potentiate tumor radiosensitivity with little or no normal tissue effect if radiation is given within 1 h of EMF exposure.

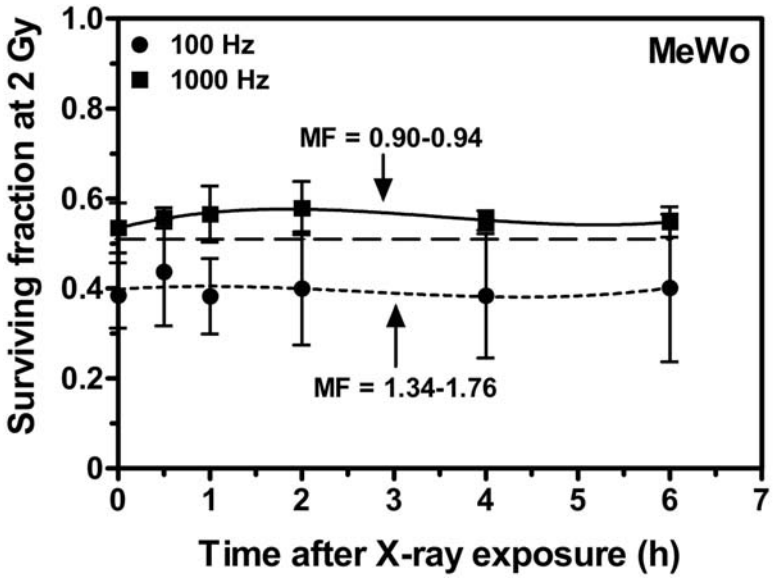

FIG. 5: Clonogenic cell survival at 2 Gy in human melanoma cells (MeWo), when cells were exposed to X-irradiation prior to a 100- or 1000-Hz–modulated 27.125 MHz carrier electromagnetic field (EMF), as a function of time between X-ray treatment and EMF exposure. Data points are means ± SEM of three independent experiments. Horizontal dashed line represents the surviving fraction at 2 Gy without EMF exposure.

Interestingly, the 100-Hz–modulated field protected and sensitized preirradiated V79 and MeWo cells, respectively (Figs. 3 and 5). This phenomenon, over all time points, indicated that exposing tumor cells to the 100-Hz–modulated field within 6 h of administering a fraction of radiation dose might have a significant level of therapeutic benefit. It is currently not clear why these cell lines behave differently when exposed to the two electromagnetic fields, and in a manner dependent on the sequence of EMF exposure and X-irradiation. However, sensitization of the cells when they are exposed to EMF followed by X-ray could be due to many different mechanisms, including the EMF causing an influx of calcium ions, with an alteration in homeostasis triggering mitotic division.[27] This process would prompt otherwise dormant cells to start dividing. Actively dividing cells are more prone to radiation-induced cell death than dormant cells, and the net effect will be a low level of cell survival. Also, the observed radiosensitization may have been caused by intracellular cascades, such as activation of matrix metalloproteinases by reactive oxygen species, the concentration of which is known to be increased by exposure to magnetic fields.[17,28] Reactive oxygen species act as radiosensitizers. Furthermore, the radiosensitization can result from calcium-ion overload, which is highly toxic and leads to cell suicide, by activating proteases and phospholipases.[18,27] Cells carrying radiation-induced DNA damage can be expected to be more radiosensitive when exposed to EMF, as the electromagnetic field can disorient

charged amino acids, resulting in a change in the three-dimensional structure of proteins and thus disturbing their function.[28] This could be a reason for the sensitization seen when cells are exposed to EMF after X-irradiation, because the enzymes responsible for repairing X-ray damage may be rendered nonfunctional by the subsequent exposure to appropriate resonant frequencies.[23] This can result in nonrepaired damage and ultimate cell death. However, this cannot explain the radiosensitization seen 6 h after X-irradiation (Figs. 3 and 5), as most all DNA repair should be completed. The radiosensitization seen when preirradiated cells were exposed to EMF may be due to dysregulation of ion channels and alteration of hormones leading to cells adopting different signaling pathways, some of which may trigger cell death.[29] Cells become more radiosensitive when more damage is inflicted on them by another form of treatment. These findings can also be attributed to cells being rendered sensitive to cell type-specific radiofrequency fields.[24]

V. CONCLUSIONS

The data reported here demonstrate that electromagnetic fields have the desirable toxic and protective effects on tumor and normal cells, respectively, if appropriate frequencies are administered at the right times relative to X-irradiation. Electromagnetic fields, therefore, have the potential of being used in conjunction with radiotherapy to reduce the total radiation absorbed dose administered to patients. This can have a significant positive impact on the management of patients with superficial tumors, especially those who are immune compromised. To fully realize the potential of this therapeutic approach, additional studies involving a broader range of cell lines are required to understand the mechanism underlying the interaction between electromagnetic fields and ionizing radiation.

ACKNOWLEDGMENTS

This work is based on research supported in part by the National Research Foundation of South Africa (Grant Numbers 85703, 92741, and 100157). Funding from the Faculty of Medicine and Health Sciences (Stellenbosch University) and the Cancer Association of South Africa is also acknowledged.

REFERENCES

1. Kaminuma T, Karasawa K, Hanyu N, Chang T-C, Kuga G, Okano N, Kubo N, Okuma Y, Nagata Y, Maeda Y, Ajisawa A. Acute adverse effects of radiation therapy on HIV-positive patients in Japan: study of 31 cases at Tokyo Metropolitan Komagome Hospital. J Radiat Res. 2010;51:749-53.
2. Jemal A, Bray F, Forman D, O'Brien M, Ferlay J, Center M, Parkin DM. Cancer burden in Africa and opportunities for prevention. Cancer. 2012;118:4372-84.
3. Goodrich JP. Experimental modification of radiosensitivity of embryonic cells. Radiology. 1943;40:179-87.

4. Potiron VA, Abderrahmani R, Clément-Colmou K, Marionneau-Lambot S, Oullier T, Paris F, Supiot S. Improved functionality of the vasculature during conventionally fractionated radiation therapy of prostate cancer. PLoS One. 2013;8(12):e84076.
5. Hamunyela R, Serafin A, Hamid M, Maleka S, Achel D, Akudugu J. A cocktail of specific inhibitors of HER-2, PI3K, and mTOR radiosensitises human breast cancer cells. J Cancer Biol Therap. 2015;1:46-56.
6. Maleka S, Serafin A, Hamunyela R, Hamid M, Achel D, Akudugu J. NVP-BEZ235 enhances radiosensitivity of human prostate cancer cells but acts as a radioprotector to normal prostate cells. J Cancer Biol Therap. 2015;1:38-45.
7. Janigro D, Perju C, Fazio V, Hallene K, Dini G, Agarwal MK, Cucullo L. Alternating current electrical stimulation enhanced chemotherapy: a novel strategy to bypass multidrug resistance in tumor cells. BMC Cancer. 2006;6:72.
8. Verginadis I, Velalopoulou A, Karagounis I, Simos Y, Peschos D, Karkabounas S, Evangelou A. Beneficial effects of electromagnetic radiation in cancer. In: Bashir SO, editor. Electromagnetic radiation. Shanghai: InTech; 2012. p. 249-68.
9. Kirson ED, Dbalý V, Tovaryš F, Vymazal J, Soustiel JF, Itzhaki A, Mordechovich D, Steinberg-Shapira S, Gurvich Z, Schneiderman R, Wasserman Y, Salzberg M, Ryffel B, Goldsher D, Dekel E, Palti Y. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A. 2007;104:10152-7.
10. Barbault A, Costa FP, Bottger B, Munden RF, Bomholt F, Kuster N, Pasche B. Amplitude-modulated electromagnetic fields for the treatment of cancer: discovery of tumor-specific frequencies and assessment of a novel therapeutic approach. J Exp Clin Cancer Res. 2009;28:51.
11. Simkó M, Kriehuber R, Weiss DG, Luben RA. Effects of 50 Hz EMF exposure on micronucleus formation and apoptosis in transformed and nontransformed human cell lines. Bioelectromagnetics. 1998;19:85-91.
12. Tofani S, Barone D, Cintorino M, de Santi MM, Ferrara A, Orlassino R, Ossola P, Peroglio F, Rolfo K, Ronchetto F. Static and ELF magnetic fields induce tumor growth inhibition and apoptosis. Bioelectromagnetics. 2001;22:419-28.
13. Sarimov R, Markova E, Johansson F, Jenssen D, Belyaev I. Exposure to ELF magnetic field tuned to Zn inhibits growth of cancer cells. Bioelectromagnetics. 2005;26:631-8.
14. Blank M, Goodman R. Electromagnetic fields stress living cells. Pathophysiology. 2009;16:71-8.
15. Goodman R, Henderson AS. Transcription and translation in cells exposed to extremely low frequency electromagnetic fields. Bioelectrochem Bioenerg. 1991;25:335-55.
16. Yamaguchi S, Ogiue-Ikeda M, Sekino M, Ueno S. Effects of pulsed magnetic stimulation on tumour development and immune functions in mice. Bioelectromagnetics. 2006;27:64-72.
17. Morabito C, Guarnieri S, Fanò G, Mariggiò MA. Effects of acute and chronic low frequency electromagnetic field exposure on PC12 cells during neuronal differentiation. Cell Physiol Biochem. 2010;24:947-58.
18. Artacho-Cordón F, Salinas-Asensio MM, Calvente I, Ríos-Arrabal S, León J, Román-Marinetto E, Olea N, Núñez MI. Could radiotherapy effectiveness be enhanced by electromagnetic field treatment? Int J Mol Sci. 2013;14:14974-95.
19. Cheing GL-Y, Li X, Huang L, Kwan RL-C, Cheung K-K. Pulsed electromagnetic fields (PEMF) promote early wound healing and myofibroblast proliferation in diabetic rats. Bioelectromagnetics. 2014;35:161-9.
20. Kirson ED, Gurvich Z, Schneiderman R, Dekel E, Itzhaki A, Wasserman Y, Schatzberger R, Paltiet Y. Disruption of cancer cell replication by alternating electric fields. Cancer Res. 2004;64:3288-95.
21. Lupke M, Frahm J, Lantow M, Maercker C, Remondini D, Bersani F, Simkó M. Gene expression analysis of ELF-MF exposed human monocytes indicating the involvement of the alternative activation pathway. BBA Mol Cell Res. 2006;1763:402-12.
22. American Cancer Society. Questionable methods of cancer management: electronic devices. CA Cancer J Clin. 1994;44:115-27.

23. Agulan RTV, Capule EMF, Pobre RF. Effect of pulsed electromagnetic fields on colon cancer cell lines (HCT 116) through cytotoxicity test. Presented at the DLSU Research Congress, vol. 3, De La Salle University, Manila, Philippines; 2015.
24. Zimmerman W, Jimenez H, Pennison MJ, Brezovich I, Morgan D, Mudry A, Costa FP, Barbault A, Pasche B. Targeted treatment of cancer with radiofrequency electromagnetic fields amplitude-modulated at tumor-specific frequencies. Chin J Cancer. 2013;32:573-81.
25. Mantiply ED, Pohl KR, Poppell SW, Murphy JA. Summary of measured radiofrequency electric and magnetic fields (10 kHz to 30 GHz) in the general and work environment. Bioelectromagnetics. 1997;18:563-77.
26. Bassen H, Litovitz T, Penafiel M, Meister R. ELF in vitro exposure systems for inducing uniform electric and magnetic fields in cell culture media. Bioelectromagnetics. 1992;13:183-98.
27. Pinton P, Giorgi C, Siviero R, Zecchini E, Rizzuto R. Calcium and apoptosis: ER-mitochondria Ca^{2+} transfer in the control of apoptosis. Oncogene. 2008;27:6407-18.
28. Lai HC, Singh NP. Medical applications of electromagnetic fields. In: Electromagnetic phenomena and health: a continuing controversy? IOP Conference Series: Earth and Environmental Science, UK: IOP Publishing; 2010. p. 10:012006.
29. Orrenius S, McCabe Jr MJ, Nicotera P. Ca^{2+}-dependent mechanisms of cytotoxicity and programmed cell death. Toxicol Lett. 1992;64/65:357-64.