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Extremely Low Frequency Electromagnetic Fields Alter Expression of C-Myc and circ-CCDC66 in Gastric Cancer Cell Line

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Abstract

The biological effects of electromagnetic fields (EMF), in particular their beneficial or adverse impacts on the promotion and progression of cancer, have attracted considerable attention. C-Myc has a critical regulatory role in cell transformation and causes metabolic changes, that accompany malignant transformation. Observations have shown that c-Myc expression can be altered by circular RNAs (circRNA). In this study, the changes in the expression of c-Myc and circ-CCDC66 in the AGS cell line after the extremely low-frequency magnetic fields (ELF-MF) exposure were investigated. The AGS cells were exposed to different magnetic flux densities for 18 h, continuously and discontinuously (2h on/2h off). To evaluate the expression changes of c-Myc and circ-CCDC66 real-time PCR was used. The results showed that discontinuous magnetic fields could reduce c-Myc expression. Continuous exposure of 0.25 mT could reduce the c-Myc expression, but with increasing the magnetic flux density c-Myc was upregulated. The expression level of circ-CCDC66 decreased under exposure to continuous and discontinuous ELF-MFs. The difference between the results of c-Myc under the influence of magnetic fields may be described by the hypothesis of the window effect of the fields. Our results indicated that ELF-MFs can induce changes in c-Myc and circ-CCDC66 expression.

Keywords: Adenocarcinoma Gastric Cell Line (AGS), Electromagnetic Field, C-Myc, circ-CCDC66

1. Background

These days, with the increasing use of electronic devices, humans have been exposed to extremely low-frequency electromagnetic fields (ELF-EMFs) with a variety of magnetic flux densities (MFDs). Recently, the biological effects of electromagnetic fields, especially their harmful or beneficial effects on different diseases, including cancer, have been studied (1, 2). The different biological effects of electromagnetic fields are directly related to their various parameters including frequency, the intensity of electromagnetic fields, and ex. The various biological impacts of electromagnetic fields are directly related to their various parameters including frequency, the intensity of electromagnetic fields, and exposure time (3). Some epidemiological studies suggest that electromagnetic fields may lead to inhibition of cancer cells (4). Electromagnetic field therapy can be used as a non-invasive and alternative method in the oncology field (5).

It has been demonstrated that the c-Myc oncogene transcripts level was increased under the exposure of ELF-EMF (6).

There is an intimate relationship between the abnormal growth of cancer cells and metabolic changes that lead to transformation. Furthermore, the significant regulatory role of c-Myc in cell transformation has been identified. C-Myc causes metabolic changes that accompany malignant transformation (7-9). It has been shown that c-Myc is activated in many types of cancer. It can also act as a transcription factor and regulator of chromatin structure (10). C-Myc contributes to the abnormal growth of transformed cells by influencing the expression of multiple gene families (11). Due to the role of the c-Myc in cancer, it can be an attractive therapeutic target. Inhibition of metabolic pathways in which the c-Myc is involved could lead to an effective way of cancer treatment (11). Observations have shown that c-Myc expression can be altered by circular

RNAs (circRNA) (12). CircRNAs are noncoding RNAs that play a critical role in the promotion and progression of cancer and can act as a biomarker of cancer. CircRNAs are involved in various biological processes such as transcription (13), mRNA splicing (14), RNA decay and translation (15). Changes in circRNA expression could induce abnormal cellular functions and various diseases including cardiovascular diseases, Alzheimer's diseases, metabolic diseases, and cancer (12, 16-18).

2. Objectives

This study aimed to evaluate the effect of ELF-MF with different MFDs of 0.25, 0.5, 1, and 2 militesla (mT) for 18 hours continuously and discontinuously (2h on/2h off) on the expression changes of c-Myc and circ-CCDC66 as a regulator of the c-Myc pathway in AGS (human gastric cancer) cell line.

3. Methods

3.1. Exposure System

The device used to create an alternative magnetic field was solenoid which was described in our previous report (19). The conditions were the same for the cells inside the solenoid. The cells were exposed to ELF continuously and discontinuously (2h on/2h off) for 18 hours (20).

3.2. Cell Culture

AGS cell lines were prepared from the Iranian Biological Resource Center. The cell culture method has been described in our previous report (20). All the cell lines were incubated at 37°C in a 5% CO2 with the water-saturated condition.

3.3. Quantitative Real-Time Polymerase Chain Reaction

To measure expression changes of c-Myc and circ-CCDC66 real-time PCR was used. RNA extraction, cDNA synthesis, and performing quantitative real-time polymerase chain reaction (qRT-PCR) were described totally in our previous report (20). The primer sequences are listed in Table 1.

Table 1. qRT-PCR Primers for c-Myc, circ-CCDC66 and the Sequences of GAPDH

Genes	Sequences
c-Myc	
Forward	5′-AACACACAACGTCTTGGAGC-3′
Reverse	5′-CCGCAACAAGTCCTCTTCAG-3′
circ-CCDC66	
Forward	5′-TCTCTTGGACCCAGCTCAG-3′
Reverse	5′-TGAATCAAAGTGCATTGCCC-3′
GAPDH	
Forward	5′-GCACCGTCAAGGCTGAGAAC-3′
Reverse	5′-GGATCTCGCTCCTGGAAGATG-3′

3.4. Statistical Analysis

SPSS software version 25 (IBM, SPSS, Chicago, USA) was used to analyze data. The experiments were performed three times in duplicate, and data are expressed as mean ± standard deviation (SD). Two-independent-sample and Mann-Whitney U test were used to evaluate the differences between the variables. Evaluation of the correlation between the variables was analyzed by the spearman test. P-value < 0.05 was considered significant.

4. Results

AGS cell lines were exposed to continuous and discontinuous ELF-MFs with MFDs of 0.25, 0.5, 1, and 2 mT. C-Myc and circ-CCDC66 expression changes under the exposure of ELF-MFs in comparison to the control group were determined by quantitative real-time PCR. Figure 1 depicts the results of expression change of c-Myc. According to the results, c-Myc was downregulated in discontinuous magnetic fields and this reduction was significant in magnetic flux densities of 0.25 (0.17 ± 0.04, $P < 0.0001$) and 0.5 mT (0.22 ± 0.02, $P < 0.0001$) when compared to control. Continuous exposure of 0.25 mT also reduce the c-Myc expression and this reduction was significant (0.22 ± 0.03, $P < 0.001$) but with increasing the magnetic flux density c-Myc was upregulated. Results showed that the expression level of c-Myc significantly increased in continuous exposure to magnetic flux densities of 1 and 2 mT (2.58 ± 0.36, $p < 0.001$ and 9.63 ± 1.6, $P < 0.001$, respectively) (Figure 2). The effect of magnetic fields on the expression level of circ-CCDC66 is shown in Figures 3 and 4. Circ-CCDC66 was downregulated to 0.014 ± 0.001 fold in 0.25 mT, 0.033 ± 0.006 fold in 0.5, 0.070 ± 0.034 fold in 1 mT and 0.11 ± 0.022 fold in 2 mT ($P < 0.001$) under the exposure of discontinuous ELF-MFs comparison with control group (Figure 4). The expression level of circ-CCDC66 decreased under the exposure of continuous ELF-MFs and was reached to 0.02 ± 0.009 fold in 0.25 mT, 0.04 ± 0.003 fold in 0.5 mT, 0.09 ± 0.023 in 1 mT and 0.12 ± 0.023 in 2 mT ($P < 0.001$) (Figure 4).

Bivariate correlation between c-Myc and circ-CCDC66 under the exposure of discontinued magnetic fields is shown in Figures 5 and 6. The circ-CCDC66 expression had a positive correlation with c-Myc ($\rho = 0.\ 8179$, $P = 0.0002$) discontinues magnetic fields, while the expression level of circ-CCDC66 did not correlate with c-Myc ($\rho = 0.3131$, $P > 0.05$) in continues magnetic fields.

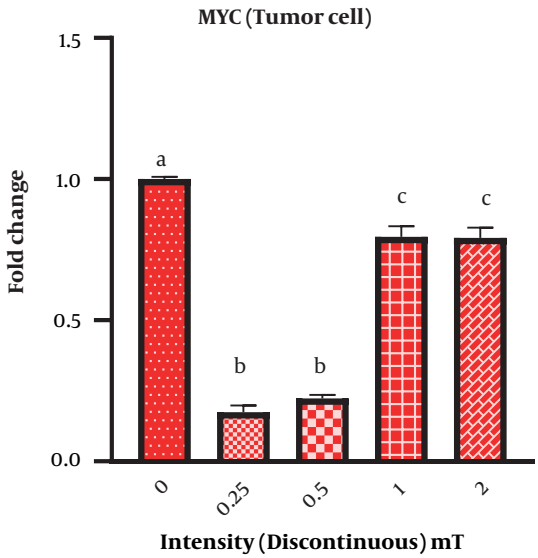

Figure 1. Expression change of c-Myc following the exposure to discontinuous ELF-EMFs in comparison to control. Data are expressed as mean ± SD (* P value < 0.05, ** P value < 0.01).

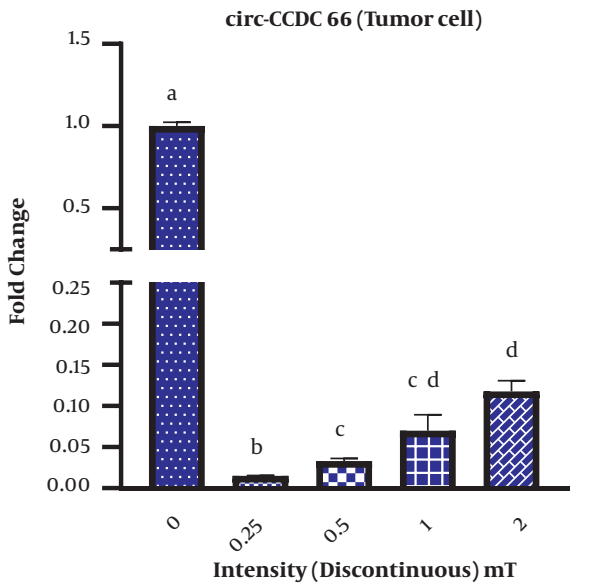

Figure 3. Expression change of circ-CCDC66 following the exposure to discontinuous ELF-EMFs in comparison to control. Data are expressed as mean ± SD (* P value < 0.05, ** P value < 0.01).

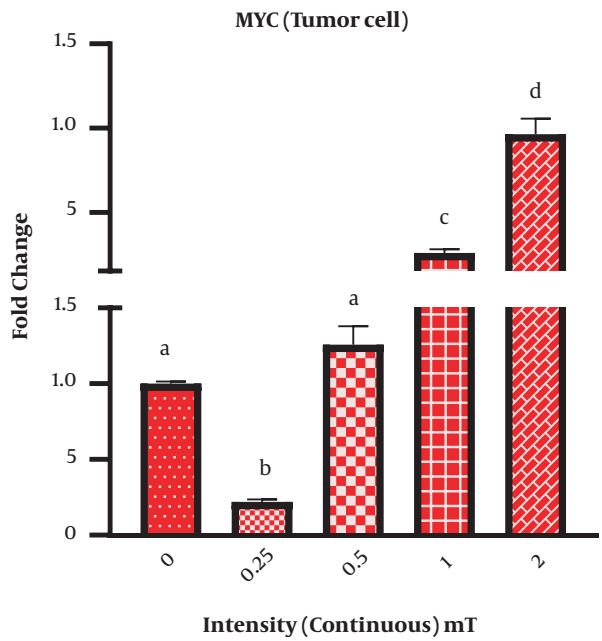

Figure 2. Expression change of c-Myc following the exposure to continuous ELF-EMFs in comparison to control. Data are expressed as mean ± SD (* P value < 0.05, ** P value < 0.01).

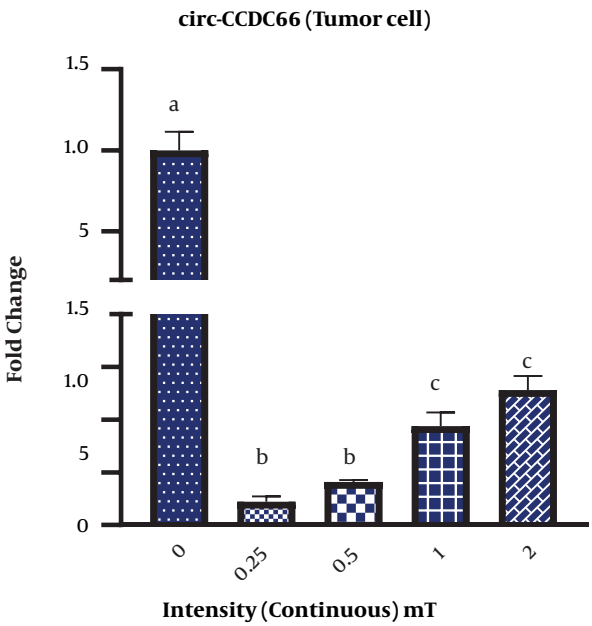

Figure 4. Expression change of circ-CCDC66 following the exposure to continuous ELF-EMFs in comparison to control. Data are expressed as mean ± SD (* P value < 0.05, ** P value < 0.01).

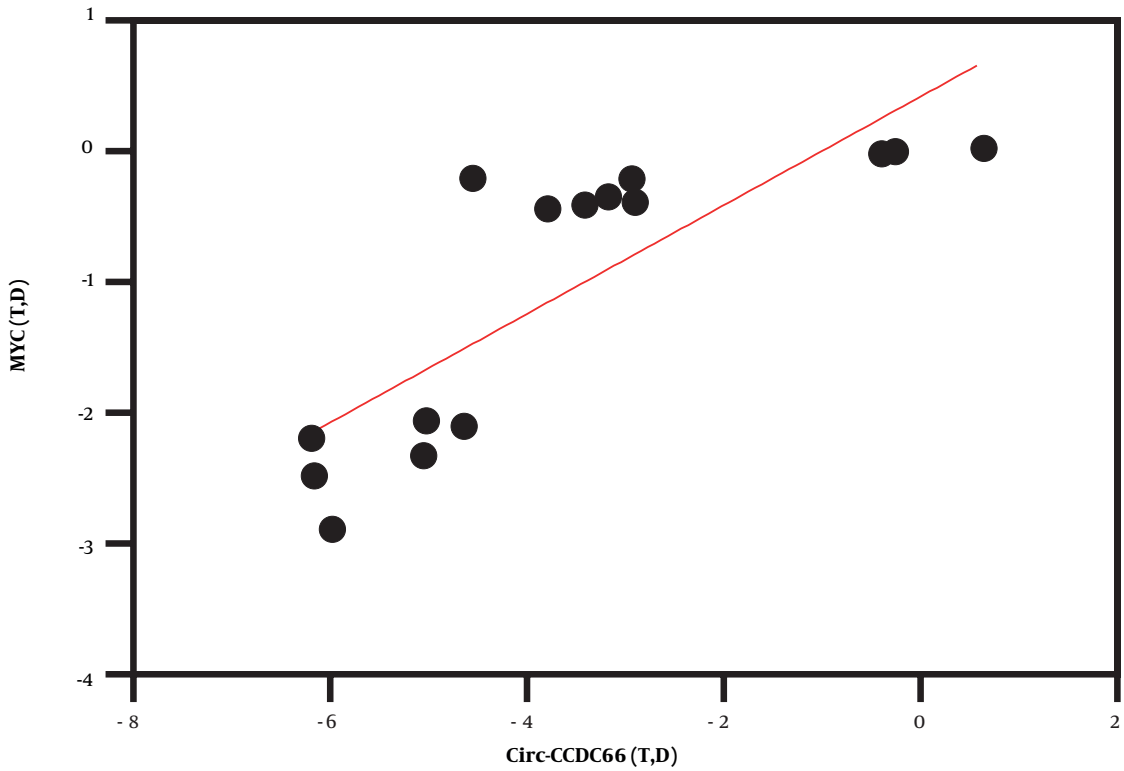

Figure 5. The correlation analysis between c-Myc and circ-CCDC66 gene expression following the exposure to discontinuous ELF-EMFs in comparison to control. Data are expressed as mean ± SD (* P value < 0.05, ** P value < 0.01).

5. Discussion

Recently, the use of ELF-MFs has been considered a safe alternative treatment for cancer (21). In this study, the effects of ELF-MFs on c-Myc and circ-CCDC66 expression changes in a gastric cell line (AGS) were evaluated. The results showed that the expression level of c-Myc decreased in discontinues ELF-MFs. Continues magnetic flux density of 0.25 mT could reduce the c-Myc expression level. In contrast, magnetic flux densities of 0.5, 1, and 2 mT induced increased c-Myc expression level. These different results of discontinues and continuous magnetic fields can be explained using the EMFs window effects hypothesis. The window is a biological response that occurs only at certain criteria of the frequency, amplitude, intensity, and time of exposure, and outside of these criteria, the biological system does not respond to EMFs (22). The expression levels of c-Myc gene in asynchronous and synchronous human cells do not change following different intensities and times of exposure to 50 Hz magnetic fields (23). Loberg et al. examined the effect of magnetic flux densities of 0.1, 1, and 10 Gauss (G) on breast tumor cells and found that c-Myc transcripts were not affected by the magnetic field (24).

C-Myc acts as a major regulator of metabolism and cell proliferation. It can be activated by several carcinogenic pathways and can also stimulate metabolic changes associated with malignancy (11). The c-Myc gene expression is normally dependent on mitogenic stimulation. C-Myc leads to cell division by driving the multiple synthetic functions. On the other hand, it inhibits the expression of genes to suppress proliferation (8, 9). Due to its ability to induce apoptosis, its oncogenic properties are tightly regulated (25). The key role of the c-Myc gene in regulating cell function makes it a therapeutic target in new cancer therapies.

Our data indicated that circ-CCDC66 expression was downregulated under the exposure of discontinuing and continuing EMFs. Circ-CCDC66 is an important regulatory network for the activation of oncogenes. C- Myc oncogene is a target for circ-CCDC66. It has been shown that circ-CCDC66 can lead to gastric cancer cells proliferation and metastasis by activating the c-Myc and TFG- β signaling pathways (12). Hsiao et al. showed that the non-coding effects of circ-CCDC66 stimulate cancer cell proliferation, migration, and metastasis (26). It has been found that circ

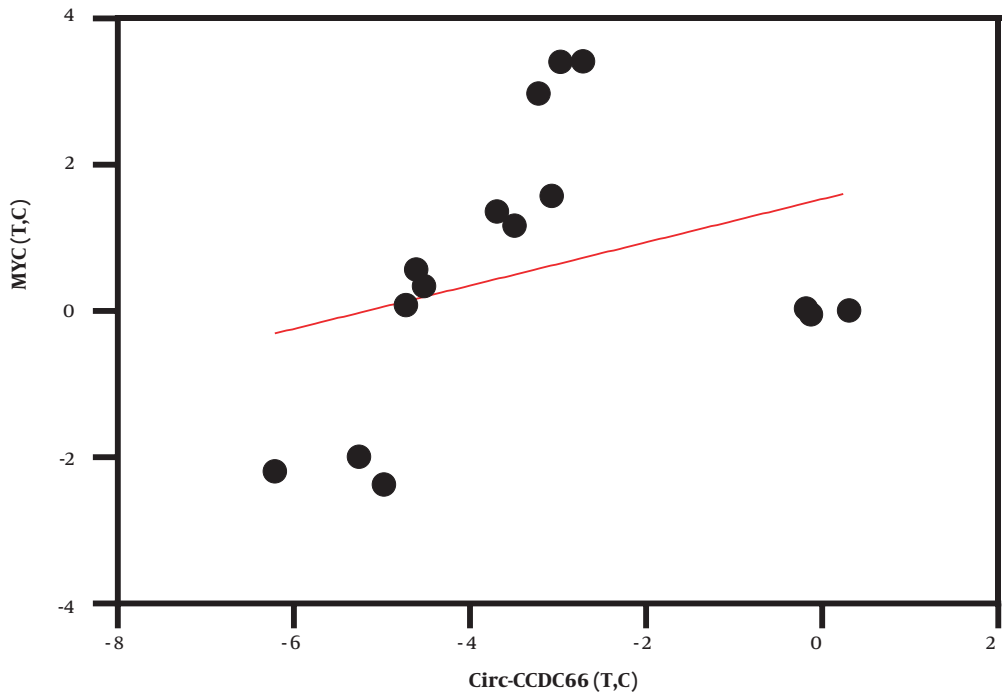

Figure 6. The correlation analysis between c-Myc and circ-CCDC66 gene expression following the exposure to continuous ELF-EMFs in comparison to control. Data are expressed as mean ± SD (* P value < 0.05, ** P value < 0.01).

CCDC66 expression is increased compared to normal cells in cervical cancer expression. The decreased circ-CCDC66 expression has also inhibited tumor cell proliferation, migration, and invasion in cervical cancer (27). Upregulation of circ-CCDC66 promotes cell proliferation and invasion in gastric cancer (28).

The biological effects of magnetic fields on living organisms depend on numerous factors such as magnetic field frequency, intensity, exposure time, and cell types (3, 29). ELF- MFs could induce DNA transcription and reduce cellular stress factor stressors through various mechanisms such as changes in membrane transport capacity, ionic channels, the lifetime of free radicals, and the electron velocity inside DNA (30, 31). The interaction of ELF- MFs with ions on the membrane leads to the induction of oscillating force and vibration of ions, which can disturb the electrochemical balance in the cell by affecting the membrane proteins, such as the calcium channel (32). Increased cytoplasmic calcium ions occur at the beginning and end of the apoptotic pathway (33). Alterations in gene expression can be caused by the acceleration of electrons within DNA due to the application of EMFs. EMFs can modulate the expression of genes that interact with DNA sequences in the promoter regions of genes (34, 35). The nCTCTn sequences on the c-Myc gene promoters act as EMFs antennae and can create a strong repulsive force within the DNA double helix and lead to the separation of the DNA chains. The repulsive force created by the EMF opposes the attraction force between the DNA strands. To balance the forces, the nCTCTn sites on the c-Myc gene promoters that are sensitive to the EMF, appear to become more separated (36). Another mechanism proposed for changes in gene expression is based on the increase of free radicals following the exposure of EMFs. This mechanism is supported by a physical effect called the Zeeman Effect (37). Studies have shown that free radicals concentration in biological systems is increased following exposure to magnetic fields (38). Oxidative stress following an increase in ROS is one of the most important causes of cell death. ROS can induce apoptosis, which is very important in the treatment of cancer (39, 40). Various studies have shown that increasing the concentration of ROS plays an important role in the effectiveness of conventional cancer treatments and is directly related to cell death (41, 42). Several studies revealed the anti-cancer effects of electromagnetic fields. Different mechanisms for the therapeutic effects of magnetic fields at the cellular level, including inhibition of angiogenesis and electrochemical modulation of cancer cells, are noteworthy (31, 43).

5.1. Conclusions

In this research, we observed a decrease in circ-CCDC66 and c-Myc in the AGS cells following the exposure to weak ELF-MFs. Activation of c-Myc by oncogenic pathways leads to metabolic changes and malignancy. Circ-CCDC66 targets c-Myc oncogene. Because of c-Myc ubiquitous role in human cancer tumor, expression changes of this oncogene could be a therapeutic target for inhibiting and controlling cancer cells growth. However, prolonged exposure to magnetic fields can adversely affect human health because the cell cycle, changes in cell proliferation, and apoptosis have not been identified in this study. More in-vitro and in-vivo studies are needed to find the optimum magnetic fields intensity.

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Footnotes

Authors' Contribution: Study concept and design, S.A.; Analysis and interpretation of data, S.A., and F. M.; Drafting of the manuscript, S. A., and N.B.; Critical revision of the manuscript for important intellectual content, S. A., F. M., and A. D.; Statistical analysis, F. M.

Conflict of Interests: One of the authors is a member of the committee board of the Journal of Human Genetics and Genomics.

Data Reproducibility: The data presented in this study are uploaded during submission as a supplementary file and are openly available for readers upon request.

Ethical Approval: This study is approved under the ethical approval code of IR. BPUMS.REC.1399.180 (link: ethics.research.ac.ir/ProposalCertificateEn.php?id=177892).

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