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miR-214 expression change in *HCT116* cancer cell line following the exposure to static magnetic fields

Soheila Abdi[1*], Fatemeh Mashayekhi[1], Amirnader Emami Razavi[2]

1 Department of Physics, Safadasht Branch, Islamic Azad University, Tehran, Iran
2 Iran National Tumor Bank, Cancer Institute of Iran, Tehran University of Medical Sciences

*Corresponding author: Department Corresponding author: Department of Physics, Safadasht Branch, Islamic Azad University, Tehran, Iran. soheilaabdi@safaiau.ac.ir , Abdi.soheila@gmail.com **Received** 2023 February 23; **Accepted** 2023 July 15.

Abstract

The Research on the effects of magnetic fields on the expression of miRNAs is helpful to understand better the mechanism of electromagnetic fields' function in the development and progression of cancer. This research investigates the effect of static magnetic fields with 1, 2, and 3 mT intensities on miR-214 expression change in the HCT-116 cell line. We used MTT assay to measure cell viability. In order to measure the expression changes of miR-214, real-time PCR was used. The results showed that the cell survival rate and expression of miR-214 had decreased significantly under the influence of magnetic fields in an intensity-dependent manner. Concerning the role of miRs in regulating signaling pathways involved in cancer promotion and progression, and their effectiveness under exposure to low-frequency magnetic fields, investigating and understanding the effects of different magnetic fields on the expression of miRs can be of great importance in preventing and controlling cancer.

Keywords: Gene expression, miR-214, Static magnetic fields, Expression change

Introduction

Due to the expansion of the use of electrical devices, appliances, cell phones, radio, and microwave technologies, the biological effects of magnetic fields (MFs) are one of the health public concerns in recent years [1]. On the other hand, many scientists have proposed magnetic fields' diagnostic and therapeutic nature. Some studies show that the interaction of MFs with living cells can enhance or reduce cancer cell activity [2, 3]. The conditions and environment of the MFs' interaction with living organisms could induce different biological effects [4]. Some research report that MFs can alter gene expression and DNA damage [5, 6]. microRNAs (miRs) are short RNA molecules with a length of 19 to 23 nucleotides. They act as the main regulators of various biological processes, including early development, cell differentiation, proliferation, and apoptosis. Therefore, changing the expression of miRs plays an essential role in the occurrence of various diseases, including cancer [7]. The role of miRs in cancer progression is well established. They often modulate cell proliferation, differentiation, migration, and invasion. Their expression is often dysregulated in different cancers, and their function varies greatly with tissue types. For example, miR-214 targets several oncogenic mRNAs, such as CD44 and CDK1, to reduce cell proliferation [8]. shown that it is a tumor suppressor in human colon cancer [9]. Increased expression of miR-15 and miR-16 and decreased BCL2 gene as a regulator of their pathway by electromagnetic fields (EMFs) have been reported before [5]. Studies have shown that MFs change the expression of the PTEN gene in gastric cancer cells, and this change depends on the intensity of the applied MFs [10].

Colon and rectal cancer is the third most popular type of cancer worldwide. The rate of this cancer increases with industrialization and urbanization. Notwithstanding advances in medical knowledge, the survival rate for colon cancer in 5-year is still less than 60% [11]. Considering the critical role of miRNAs in cancer, research on the effects of magnetic fields on the expression of miRNAs is helpful to understand better the mechanism of electromagnetic fields' function in the development and progression of cancer. This research investigates the effect of static magnetic fields (SMFs) with 1, 2, and 3 mT intensities on miR- 214 expression change in the HCT116 cancer cell line.

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Materials and Method

Magnetic field generator System

The magnetic field was generated in a solenoid designed in our previous research. The cells were exposed to static magnetic fields with the same condition [12].

Cell Culture

HCT116 colon cancer cell line was cultured in DMEM/F12 media containing 10% FCS, 100 units/ml penicillin G, and 100 µg/ml streptomycin. HCT116 cells were cultured in serum-free DMEM/F12 media [13]

MTT assay

We used MTT assay to measure the cell viability, which we thoroughly explained in our previous study [4].

qRT- PCR

We used real-time PCR to measure expression changes of miR-214. In our last study, we explained RNA extraction, cDNA synthesis, and performing qRT-PCR [4].

Statistical calculations

Statistical calculations were performed by SPSS software version 25 (IBM, SPSS, Chicago, USA). In order to measure the differences between the variables, a two-independent-sample, and Mann-Whitney U test were used. P-value < 0.05 was considered significant.

Results and Discussion

Figure and Table 1 show the results of MTT Assay analysis. The results show that the cell survival rate has decreased under the influence of magnetic fields, and this reduction is significant. The role of miR- 214 as an oncogene in colon cancer progression has been accepted. This study evaluated the changes in miR-214 expression under the influence of a static magnetic field with weak and medium intensities of 0.5, 1, and 3 mT. For this purpose, magnetic flux densities of 0.5, 1, and 3 mT affected the colon cancer cell line for 18 hours. Cell survival was measured by the MTT method, which showed a significant decrease compared to the control sample. Scientific research on EMF interactions with living systems, especially health effects, is increasing. There are arguments for both positive and negative effects. However, insufficient knowledge about the biological effects of most frequencies leads to concern. The debate, especially on non-thermal effects, is still ongoing. Figure 2 shows the results of miR-214 expression change. As can be seen from the results, the expression of miR- 214 has decreased significantly under the influence of magnetic fields. Earth's electromagnetic environment is rapidly changing due to human-made technological advances. Electromagnetic waves provide countless benefits and, on the other hand, can create potential dangers by releasing uncontrollable and excessive radiation. The biological effects of external magnetic fields have received widespread attention over the decades [14]. In general, three main biological mechanisms are the most critical mechanisms of EMF action on the cell: 1) effects on the cell membrane, 2) effects on the free radical concentration in the cell, and 3) effects on the intracellular regulatory systems [15]. The cell membrane is about 6-10 nm thick, supporting a robust bipolar layer. From a physical point of view, in the complex structure of the cell surface, local vibrations of a part of the cell membrane are possible so that the positive and negative charges of a specific part of the membrane vibrate against each other and create an oscillating electric dipole [15]. Low-frequency electric or magnetic fields create electric currents in the body, leading to nerve stimulation [16]. Research has shown that low-frequency magnetic fields can affect the transport of calcium ions across cell membranes [17]. Calcium is an important signaling substance in the living cell, and disruption of its cellular balance may disrupt many cell functions. Therefore, the cell membrane is believed to be an essential site of interaction with electromagnetic fields [17]. New studies have confirmed the increase of intracellular Ca+2 following exposure to EMF. The most critical parameter connecting Ca+2 homeostasis with apoptosis is the increase in the cytosolic Ca+2 level [18]. Free radicals that exist in cells play an essential role in intracellular processes. These compounds can react with cellular structures and cause their destruction, so their high amount is undesirable. Excess free radicals can cause mutations and apoptosis. Increasing their concentration causes oxidative stress and subsequent damage to ion channels and changes in cell morphology, gene expression, apoptosis, and proliferation [19]. Low-frequency EMFs induce oxidative stress [20]. Oxidative stress produced by EMFs can have different adverse effects, from micronucleus formation to DNA strand breaks [20, 21]. Magnetic fields are believed to activate the DNA by generating oscillating forces while accelerating the electrons inside the helix of the two strands. Since magnetic fields penetrate the cell, they can directly interact with DNA in the nucleus or mitochondrial DNA. CTCT sequences, which are called electromagnetic field responsive elements (EMRES), can act as sensors or antennas on the promoter of c-myc and Hsp70 genes [22]. It can be assumed that the initiation of transcription by magnetic fields depends on the field's interaction with the movement of electrons in DNA to produce oscillatory forces that lead to DNA chain separation. Therefore, the electron density of each base can affect the speed of electron movement. Based on this, the regions rich in C and T in the DNA strand can be known as sequences sensitive to magnetic fields [22]. It should be noted that microwave EMFs can stimulate the transcription and production of HSP in cells and organisms [23]. HSP is a heat shock protein that can affect cell cycle progression[23]. When conditions are unfavorable for successful cell proliferation, for example, high levels of DNA damage, low nutrients, hypoxia, viral genome activation, and cell arrest in the G1, G2, or M phase of the cell cycle, cell quiescence creates the conditions for activation of the defensive machinery or survival [23]. If there is a severe imbalance in intracellular conditions, apoptosis is initiated, and HSP affects cell cycle progression. It has been shown that magnetic fields at very low frequencies can act as a stress factor in various systems. Exposure to ELF can induce a robust biological response, such as increased expression of stress-associated HSPs [24, 25]. In general, exposure to magnetic fields will cause changes in the cell cycle and, ultimately, cell proliferation. In co-phase cells, this leads to a delay in the cell cycle, which can cause defects and reduced proliferation [24, 25]. In non-synthase cells, this leads to homophase and increased proliferation. However, when the damaged DNA is repaired, the magnetic field-induced HSP is broken down, and the normal cell cycle resumes. Another pathway to resume

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the normal cell cycle is eliminating cells with defective DNA through apoptosis by the activated p53 pathway. p53 activity is inhibited in many types of cancer cells, preventing the apoptosis of defective cells [26]. Exposure to EMFs can inactivate the p53 apoptotic pathway [26]. In the case of HSP production through oxidative stress or other stressors, the HSP response decreases with repeated exposure, and thus a more significant amount of stress is required to elicit the same HSP response [25]. In addition, repeated exposure to RF/EMF can also lead to defective cell proliferation due to the lack of HSP response [27, 28]. The use of EMF in therapy has a long history. For example, modern medical applications of EMF are used to heal broken bones and wounds and some bone-related diseases through the stimulation of osteogenesis [29, 23]. It has been proven that the magnetic field with different intensities, from mT to T, affects different activities of cancer cells. The inhibitory effect has been observed, especially in the growth of cancer cells. Apoptosis in cancer cells has been observed due to increased free radical concentration following static magnetic fields [21]. Yong et al. investigated the effect of magnetic fields on the regulatory mechanisms of miR expression profile in mouse spermatocyte cells [30]. In short, magnetic fields change the expression of miRs. The regulation of signaling pathways of miRs can play an essential role in the biological effects of low-frequency magnetic fields.

Research indicated that miR-214 is downregulated in colon cancer, and also it was shown that miR-214 has a role in reducing the proliferation and migration of HCT-116 cancer cells [26]. Therefore, the reduction of miR-214 expression due to SMF applied in this study can be considered a risk factor in colon cancer, although the proof of this hypothesis requires more extensive research in other cell lines in-vitro and in-vivo. Especially since researchers have shown that magnetic fields can have extensive effects on different metabolic pathways and in various ways, investigating and estimating the results of these effects together requires much more extensive investigation.

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Table 1. Changes of colon cancer cell viability following the exposure to static magnetic fields in comparison to control; data are expressed as mean ± SD; ∗ = p-value < 0.05, OD = optical density of absorbance

MFD	OD	P value
Control	0.50 ± 0.008	
0.5 mT	0.48 ± 0.009	0.004
1 mT	0.43 ± 0.016	0.000
3 mT	0.38 ± 0.008	0.000

Data are expressed as mean ± SD. P value < 0.05 are considered statistically significant. *MFD*= magnetic flux density

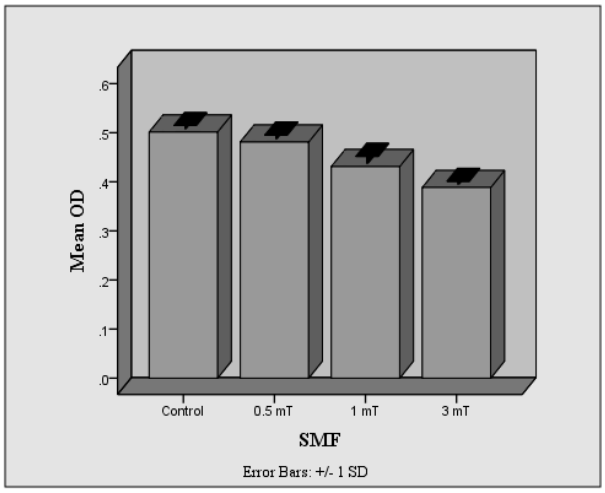

Figure 1. Changes of colon cancer cell viability following the exposure to static magnetic fields in comparison to control; data are expressed as mean ± SD; ∗ = p-value < 0.05, OD = optical density of absorbance.

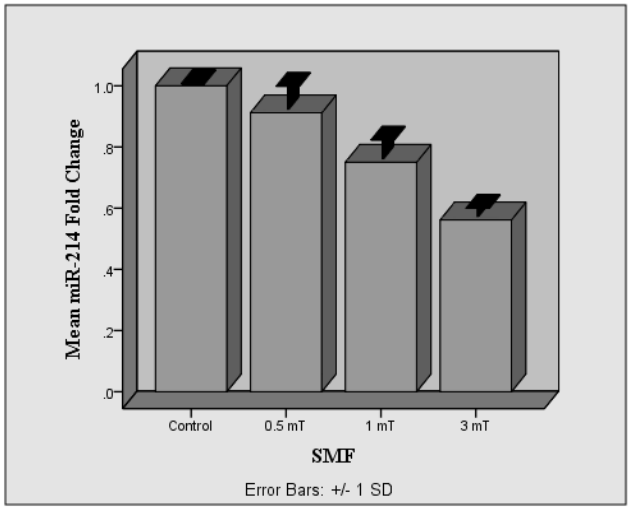

Figure 2. Expression changes of miR-214 following the exposure to static magnetic fields in comparison to control; data are expressed as mean ± SD; ∗ = p-value < 0.05, ∗∗ = p-value < 0.01.

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