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# Possible Curative Role of Electromagnetic Field on Cancer Treatment and Link to Temozolomide Resistance and MGMT

**Zaka Abbaszade[1*], Alihaydar Kaygusuz[1], Suleyman Kamilov[2], Vahidreza Karamad[1] and Morteza Haghi[3]**

[1]Ege University, Faculty of Medicine, Department of Medical Biology. Bornova/İzmir, Turkey

[2]Central hospital of oil workers, Baku, Azerbaijan

[3]EDGE Food & Feed & Environmental Research Laboratory İzmir/Turkey

**ABSTRACT**

One of the mechanisms that has an important role in the differentiation of stem cells into more specialized cell types during embryonic development is the methylation of genomic DNA. Like other epigenetic mechanisms, DNA methylation also functions as the interface of control unit of DNA-protein relationship after embryonic development and even at all stages of ontogeny. For this reason, errors that occur in the realization of DNA methylation in embryogenesis and ontogeny appear as different pathologies and are reflected in the clinic as different diseases. It is known that the application of electromagnetic field (EMF) has a healing and supportive effect on human health with studies conducted in different fields of medicine. The effects of the electromagnetic field on cancer cells have also been evaluated from different perspectives by numerous studies. One of these important effects is the effects that occur at the epigenetic level. In addition, the effect of temozolomide (TMZ), which is an important agent used in cancer treatment, is directly related to epigenetic mechanisms and net DNA methylation. There are some deficiencies in the studies conducted on this subject. For example, the extent to which the O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is affected while the electromagnetic field affects cancer cells. No any significant data exist about the effect of electromagnetic field on MGMT promoter methylation. The aim of this study is to pay attention on whether EMF can affect promoter methylation and whether MGMT promoter methylation is being affected from it.

***Corresponding author**

Zaka Abbaszade, Ege University, Faculty of Medicine, Department of Medical Biology. Bornova/İzmir, Turkey. E-mail: zekaabbaszadeh@gmail.com

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## Introduction

Electromagnetic field has impact on different types of cells in the human organism. The effects of electromagnetic field in various frequencies has not been fully declared biologically. Because EMF may not cause direct damage to cell organelles and DNA every time. Cells exposed to low and extremely low electromagnetic field has observed to have oxidative damage. According to numerous in vitro studies demonstrated that electromagnetic field can affect cancer cell growth and development. According to Wolf et al. 50Hz electromagnetic field stimulates DNA damage [1-3].

Pulsed electromagnetic field (PEMF) can regulate tumor supressors and oncogenes through epigenetic mechanisms. Low frequency EMF has shown to be impressed normal cells and cancer cells through establishing DNA damage by the action of free radicals. According to Pasi et al. PEMF reveals pro apoptotic impact on radioresistant glioblastoma cell line. PEMF has observed to trigger autophagy after exposure of 2 mT EMF at frequency of 75 Hz. 60-Hz sinusoidal MF applied to three different kinds of prostate cancer cells suppressed cell growth and triggered apoptosis in vitro. EMF has shown to cause increase of ROS and phagocytosis has also joined this process. Besides these mechanisms it has also observed that EMF affects epigenetic equipment of cell through altering methylation levels of DNA and therefore promoter regions of genes plays important role on cancer proliferation and development [3-6].

## The Role of Alkylating Agents and Temozolomide

Alkylating agents are important and most used anticancer agents. Action mechanisms of most alkylating agents are similar; affects directly on DNA through adding alkyl groups to guanine base and making crosslinks. It causes strand breaks in DNA and abnormal base pairing in DNA double strand causing proliferation inhibition. One of the most promising therapeutic agent especially for brain tumors is temozolomide (TMZ). TMZ is a small (194 Da) lipophilic molecule, is an orally available monofunctional DNA alkylating agent of the imidazotetrazine class. Temozolomide is an oral alkylating agent that is effective on prolonging survival, slowing the development and growth of cancer cells when administered during and after radiotherapy. Temozolomide has been authorised by US FDA (Food and Drug Administration) as drug. İt is priority choice for conventional chemoteraphy for GBM [7-10].

## The Role of Methylation and MGMT Temozolomide Relationship

DNA methylation is a crucial epigenetic mechanisms of mammalian cells. It occurs through the transfer of the methyl

group to the cytosine amino acid residues of CpG dinucleotides at C5 position. Through DNA methylation, gene expression is being controlled and regulated by numerous factors, that act epigenetic functions. DNA methylation can inhibit expression of genes that codes proteins by methylating their promoter region. Methylation level, raised abnormally in promoter regions of genes, come across in various cancers and one of the factors causing cancer. This enzymatic reaction catalyzed by DNA methyltransferases (DNMTs). It is known that DNMTs are significantly elevated in many tumor species such as breast, colon, endometrial, prostate, stomach and uterine cancers [11,12].

O6-methylguanine-DNA methyltransferase (MGMT) first discovered in Escherichia coli, sequentially mammals and other eukaryotes. It's a suicide enzyme. The gene sequence of MGMT Located on chromosome 10 at the 10q26 position and highly conserved during evolution. MGMT is an alkyl-group acceptor. After detecting an alkyl (methyl) radical on DNA addition at the O6 position of guanine, MGMT cuts out alkyl group through transferring it onto sulfur residue on its acceptor site. In the promoter region of MGMT have no TATA-box and CAAT-box and rich in GC nucleotides carve out CpG islands. MGMT promoter methylation is a positive indicator in glioblastoma patients. Because MGMT promoter methylation enhances sensitivity in GBM patients to TMZ treatment [13-16].

**Effects of Electromagnetic Field and Temozolomide in Cancer**

Due to importance of DNMTs on methylation pattern of cancer cells and their role in various cancers, it becomes conspicious for predictive studies. A study carried out by Yong Liu et al. demonstrated that GC-2 cells exposed magnetic field at 1mT, 2mT, and 3mT intensities led to global DNA methylation in during 72 hours. EMF methylation of GC-2 cells decreases at low magnetic intensity (1mT) compared to higher magnetic intensity (3mT). Epigenetic changes play roles in 50 Hz ELF-EMF, so it can change methylation and expression levels of DNMTs. This study carried out with GC-2 cells is also one of the rarest study that put forth the impact of extremely low EMF on global DNA methylation. PMF In combination with oxidative stress decreases DNA methylation at CpG units in comparison with oxidative stress effect alone. Only one study exists which combination of temozolomide and EMF are applied to GBM cell lines with methylated and unmethylated promoter of MGMT. But no significantly difference has been observed between both cells with methylated and unmethylated MGMT. According to Kirson et al. magnetic field can sensitizes cells against TMZ and implicitly can reduce or bypass its resistance. 100 Hz of EMF has shown to increase significantly the cytotoxicity of 100 mM TMZ. In addition, this indicates that there is a significant synergistic effect between TMZ and EMF. A study at phase 3 clinical trial indicated that application of 200 kHz of magnetic field combined with conventional TMZ therapy for glioblastoma improved progression free survival and overall survival. According to Dehghani-Soltani et al. the combination of TMZ and EMF raises cell death in T98 and A172 cell lines. But in A172 cells the MGMT was not been expressed. It raises another question. Whether magnetic field affects promoter methylation of MGMT or simply decreases the expression of MGMT. In another clinical study, magnetic field application was added in parallel with the temozolomide treatment applied to patients with methylation in the MGMT promoter region with a higher survival rate and no methylation in the promoter region with a lower survival rate. As a result of the study, it was observed that the survival rate increased in both patient groups. This and similar limited studies show that the effectiveness of temozolomide in the relationship between temozolomide and MGMT increases with the application of magnetic field. However, none of these studies reveal any facts about whether the magnetic field affects MGMT promoter methylation [17].

**Conclusion**

According to studies, temozolomide, which is an alkylating agent, requires high doses because its effect is weakened by some resistance mechanisms. O6-methylguanine-DNA methyltransferase (MGMT), a DNA repair protein, is the most important factor in this resistance to alkylating agents and of course TMZ. Therefore, in order to reduce the effective dose of TMZ and increase its effect, there is a need for auxiliary mechanisms that can affect MGMT promoter methylation and new methods to be used in combination with TMZ. It has been revealed that the effect of the applied low-frequency electromagnetic field on the efficacy of temozolomide is possible. It is also known that magnetic field has a significant effect on DNA methylation. However, there is no clear data in the literature showing that the effect of the electromagnetic field on temozolomide by combining these two features is precisely due to the MGMT promoter region methylation. Our prediction consists of increasing the effect of temozolomide by increasing the methylation levels by applying a low or extremely low magnetic field, which is a non-invasive and less harmful method. Therefore, although there are sufficient studies indicating that the electromagnetic field causes DNA methylation, there is only one study on whether this methylation occurs in the MGMT promoter region. Due to the lack of studies on this subject, prospective studies are needed in order to shed light on the effect of magnetic field on MGMT promoter methylation.

**Conflict of Interest Statement**

The authors declare that there is no conflict of interest.

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