Calcium -Magnetic Fields

https://pubmed.ncbi.nlm.nih.gov/19667166/
Calcium, vitamin D and cancer 2009
A low vitamin D status and inadequate calcium intake are important risk factors for various types of cancer. Ecological studies using solar UV-B exposure as an index of vitamin D3 photoproduction in the skin found a highly significant inverse association between UV-B and mortality in fifteen types of cancer. Of these, colon, rectal, breast, gastric, endometrial, renal and ovarian cancer exhibit a significant inverse relationship between incidence and oral intake of calcium. In addition, lung and endometrial cancer as well as multiple myeloma are considered calcium and vitamin D sensitive

https://pubmed.ncbi.nlm.nih.gov/25875081/
Inhibition of cancer cell growth by exposure to a specific time-varying electromagnetic field involves T-type calcium channels 2015
Electromagnetic field (EMF) exposures affect many biological systems. The reproducibility of these effects is related to the intensity, duration, frequency, and pattern of the EMF. We have shown that exposure to a specific time-varying EMF can inhibit the growth of malignant cells. Thomas-EMF is a low-intensity, frequency-modulated (25-6 Hz) EMF pattern. Daily, 1 h, exposures to Thomas-EMF inhibited the growth of malignant cell lines including B16-BL6, MDA-MB-231, MCF-7, and HeLa cells but did not affect the growth of non-malignant cells. Thomas-EMF also inhibited B16-BL6 cell proliferation in vivo. B16-BL6 cells implanted in syngeneic C57b mice and exposed daily to Thomas-EMF produced smaller tumours than in sham-treated controls. In vitro studies showed that exposure of malignant cells to Thomas-EMF for > 15 min promoted Ca(2+) influx which could be blocked by inhibitors of voltage-gated T-type Ca(2+) channels. Blocking Ca(2+) uptake also blocked Thomas-EMF-dependent inhibition of cell proliferation. Exposure to Thomas-EMF delayed cell cycle progression and altered cyclin expression consistent with the decrease in cell proliferation. Non-malignant cells did not show any EMF-dependent changes in Ca(2+) influx or cell growth. These data confirm that exposure to a specific EMF pattern can affect cellular processes and that exposure to Thomas-EMF may provide a potential anti-cancer therapy.

https://pubmed.ncbi.nlm.nih.gov/38143305/
Induction of apoptosis in B16-BL6 melanoma cells following exposure to electromagnetic fields modeled after intercellular calcium waves 2024
Exposure to time-varying electromagnetic fields (EMF) has the capacity to influence biological systems. Our results demonstrate that exposure to time-varying EMF modeled after the physiological firing frequency of intercellular calcium waves can inhibit proliferation and induce apoptosis in malignant cells. Single exposure of B16-BL6 cells to a Ca2+ EMF for 40 min reduced the number of viable cells by 50.3%. Cell imaging with acridine orange and ethidium bromide dye revealed substantial cellular apoptosis, preapoptotic cells, nuclear fragmentation, and large spacing between cells in the Ca2+ EMF condition when compared to the control condition. The ability of Ca2+ EMF to influence the proliferation and survival of malignant cells suggests that exposure to specific EMF may function as a potential anticancer therapy.

https://pubmed.ncbi.nlm.nih.gov/33111597/
Inhibition of B16F10 Cancer Cell Growth by Exposure to the Square Wave with 7.83+/-0.3Hz Involves L- and T-Type Calcium Channels 2021
Extremely low-frequency electromagnetic field (ELF-EMF) exposure influences many biological systems; these effects are mainly related to the intensity, duration, frequency, and pattern of the ELF-EMF. In this study, exposure to square wave with 7.83±0.3 Hz (sweep step 0.1 Hz) was shown to inhibit the growth of B16F10 melanoma tumor cells. In addition, the distribution of the magnetic field was calculated by Biot-Savart Law and plotted using MATLAB. In vitro studies demonstrated a decrease in B16F10 cell proliferation and an increase of Ca2+ influx after 48 h of exposure to the square wave. Ca2+ influx was also partially blocked by inhibition of voltage-gated L- and T-type Ca2+ channels. The data confirmed that the specific time-varying ELF-EMF had an anti-proliferation effect on B16F10 cells and that the inhibition is related to Ca2+ and voltage-gated L- and T-type Ca2+ channels.

https://pubmed.ncbi.nlm.nih.gov/36976089/
Intermittent Exposure to a 16 Hz Extremely Low Frequency Pulsed Electromagnetic Field Promotes Osteogenesis In Vitro through Activating Piezo 1-Induced Ca2+ Influx in Osteoprogenitor Cells 2023
Exposure to extremely low frequency pulsed electromagnetic fields (ELF-PEMF) is supposed to simulate local EMF generated during mechanical stimulation of bone and may therefore be used to improve bone regeneration. This study aimed at optimizing the exposure strategy and investigating the underlying mechanisms of a 16 Hz ELF-PEMF, previously reported to boost osteoblast function. Comparing influences of daily continuous (30 min every 24 h) and intermittent (10 min every 8 h) exposure to the 16 Hz ELF-PEMF on osteoprogenitor cells revealed that the **intermittent exposure** strategy enhanced the 16 Hz ELF-PEMF effects regarding cell numbers and osteogenic function. Gene expression of piezo 1 and related Ca2+ influx were significantly increased in SCP-1 cells with the daily intermittent exposure. Pharmacological inhibition of piezo 1 with Dooku 1 largely abolished the positive effect of the 16 Hz ELF-PEMF exposure on osteogenic maturation of SCP-1 cells. In summary, the intermittent exposure strategy enhanced the positive effects of 16 Hz continuous ELF-PEMF exposure in terms of cell viability and osteogenesis. This effect was shown to be mediated by an increased expression of piezo 1 and related Ca2+ influx. Thus, the intermittent exposure strategy is a promising way to further optimize the therapeutic effects of the 16 Hz ELF-PEMF regarding fracture healing or osteoporosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5119968/
Mechanisms and therapeutic effectiveness of pulsed electromagnetic field therapy in oncology 2016
During immediate PEMF exposure in undifferentiated PC12 cells, no change in intracellular Ca2+ concentration was observed, while it increased after long-term exposure. This enhanced calcium level could activate, through voltage-gated (L-type) calcium channels, signaling pathways and lead to the expression of genes modulating cell differentiation, survival, and apoptosis such as extracellular signal-regulated kinases, c-Jun N-terminal protein kinase/stress-activated protein kinase, and p38 70, 71, 72, 73. In particular, the undifferentiated PC12 cells were more sensitive to PEMFs exposure, while the differentiated PC12 cells were more stable and resistant to stress, probably due to the action of the cell surface NGF

receptors such as p75NR 74.

https://pubmed.ncbi.nlm.nih.gov/20005945/
Modulation of redox status and calcium handling by extremely low frequency electromagnetic fields in C2C12 muscle cells: A real-time, single-cell approach 2009
The biological effects of electric and magnetic fields, which are ubiquitous in modern society, remain poorly understood. Here, we applied a single-cell approach to study the effects of short-term exposure to extremely low frequency electromagnetic fields (ELF-EMFs) on muscle cell differentiation and function using C2C12 cells as an in vitro model of the skeletal muscle phenotype. Our focus was on markers of oxidative stress and calcium (Ca(2+)) handling, two interrelated cellular processes previously shown to be affected by such radiation in other cell models. Collectively, our data reveal that ELF-EMFs (1) induced reactive oxygen species production in myoblasts and myotubes with a concomitant decrease in mitochondrial membrane potential; (2) activated the cellular detoxification system, increasing catalase and glutathione peroxidase activities; and (3) altered **intracellular Ca(2+)**homeostasis, increasing the spontaneous activity of myotubes and enhancing cellular reactivity to a depolarizing agent (KCl) or an agonist (caffeine) of intracellular store Ca(2+)channels. In conclusion, our data support a possible link between exposure to ELF-EMFs and modification of the cellular redox state, which could, in turn, **increase the level of intracellular Ca(2+)**and thus modulate the metabolic activity of C2C12 cells.

https://pubmed.ncbi.nlm.nih.gov/37194107/
Electromagnetic fields regulate calcium-mediated cell fate of stem cells: osteogenesis, chondrogenesis and apoptosis 2023
Electromagnetic fields (EMF) are increasing in popularity as a safe and non-invasive therapy. On the one hand, it is widely acknowledged that EMF can regulate the proliferation and differentiation of stem cells, promoting the undifferentiated cells capable of osteogenesis, angiogenesis, and chondroblast differentiation to achieve bone repair purpose. On the other hand, EMF can inhibit tumor stem cells proliferation and promote apoptosis to suppress tumor growth. As an essential second messenger, intracellular calcium plays a role in regulating cell cycle, such as proliferation, differentiation and apoptosis. There is increasing evidence that the modulation of intracellular **calcium ion** by EMF leads to differential outcomes in different stem cells. This review summarizes the regulation of channels, transporters, and ion pumps by **EMF-induced calcium oscillations**. It furtherly discusses the role of molecules and pathways activated by EMF-dependent calcium oscillations in promoting bone and cartilage repair and inhibiting tumor stem cells growth.
We believe that the two-sided ability of EMF to promote stem cells differentiation and tumor stem cells apoptosis is due to three reasons: first, EMF as an energy field promotes the opening of ion channels and the inward flow of calcium ion when we use lower frequencies and appropriate intensities [20, 53, 54], and causes calcium overload when the electromagnetic field intensity or frequency is further increased [21,22,23,24], second, EMF can regulate multiple ions in cells, and calcium ion play a key role [92, 130], calcium ion acts as a second messenger that can activate downstream molecules such as NO, ROS [77, 100, 102, 106],which further regulate cell differentiation or apoptosis through the β-catenin pathway; thirdly, the variation of calcium channels in tumor stem cells themselves, which makes the regulation of EMF polarized [131] (Fig. 4).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4397079/
Inhibition of Cancer Cell Growth by Exposure to a Specific Time-Varying Electromagnetic Field Involves T-Type Calcium Channels 2015
Electromagnetic field (EMF) exposures affect many biological systems. The reproducibility of these effects is related to the intensity, duration, frequency, and pattern of the EMF. We have shown that exposure to a specific time-varying EMF can inhibit the growth of malignant cells. Thomas-EMF is a low-intensity, frequency-modulated (25-6 Hz) EMF pattern. Daily, 1 h, exposures to Thomas-EMF inhibited the growth of malignant cell lines including B16-BL6, MDA-MB-231, MCF-7, and HeLa cells but did not affect the growth of non-malignant cells.
Much attention has focused on the ability of low-frequency (<300 Hz) magnetic fields with simple or symmetrical (sine- or square-wave) patterns to affect cellular processes [11–13]. Some studies have shown that exposure to a low frequency EMF pattern can promote cell proliferation [5,14] while others have shown that EMF exposure inhibits cell proliferation [15–17]. Exposure of cells to 20–60 Hz EMF patterns has been shown to affect signal transduction pathways with effects on cAMP levels, MAP kinase activation, Ca2+-calmodulin kinase activation, or Ca2+ channels being the most commonly reported [11, 18–20].

https://pubmed.ncbi.nlm.nih.gov/38356636/
Modulation of calcium signaling and metabolic pathways in endothelial cells with magnetic fields 2024
Calcium signaling plays a crucial role in various physiological processes, including muscle contraction, cell division, and neurotransmitter release. Dysregulation of calcium levels and signaling has been linked to a range of pathological conditions such as neurodegenerative disorders, cardiovascular disease, and cancer. Here, we propose a theoretical model that predicts the modulation of calcium ion channel activity and calcium signaling in the endothelium through the application of either a time-varying or static gradient magnetic field (MF). This modulation is achieved by exerting magnetic forces or torques on either biogenic or non-biogenic magnetic nanoparticles that are bound to endothelial cell membranes. Since calcium signaling in endothelial cells induces neuromodulation and influences blood flow control, treatment with a magnetic field shows promise for regulating neurovascular coupling and treating vascular dysfunctions associated with aging and neurodegenerative disorders. Furthermore, magnetic treatment can enable control over the decoding of Ca signals, ultimately impacting protein synthesis. The ability to modulate calcium wave frequencies using MFs and the MF-controlled decoding of Ca signaling present promising avenues for treating diseases characterized by calcium dysregulation.

https://www.nature.com/articles/nrc.2017.18
The calcium–cancer signalling nexus 2017
Calcium is a ubiquitous but nuanced cellular signal; it regulates functions as diverse as cell motility, cell division and cell death. Precise control of the temporal and spatial aspects of calcium changes enable the signal to achieve specific cellular outcomes.
The nature of the calcium signal is controlled by a diverse array of calcium channels and pumps, and exchangers present on the plasma membrane and membranes of intracellular organelles. Certain cancers are associated with the remodelling of the expression of some of these proteins.

Calcium channels and pumps are amenable to targeting by pharmacological agents.
Calcium and calcium-regulating proteins contribute to many of the processes key to cancer cells, including proliferation, invasion and cell death.
Several oncogenes and tumour suppressors have effects on calcium homeostasis.
Calcium signalling in the tumour microenvironment is likely to be a complex interplay between several different stromal cell types and cancer cells and represents new opportunities for therapeutic intervention.
The calcium signal is a crucial regulator of processes associated with tumour progression, including epithelial to mesenchymal transition and the acquisition of specific pathways important in therapeutic resistance.
The application of new methods to assess calcium signalling in vivo and over long periods of time will provide new insights into the remodelling of calcium signalling in cancer.

https://onlinelibrary.wiley.com/doi/abs/10.1002/bem.22181
Involvement of calcium in 50-Hz magnetic field-induced activation of sphingosine kinase 1 signaling pathway
In the present study, the possible signaling pathways which were involved in SK1 activation induced by 50-Hz MF exposure were investigated. Results showed that MF exposure increased intracellular Ca^{2+} which was dependent on the L-type calcium channel, and induced Ca^{2+}-dependent phosphorylation of extracellular regulated protein kinase (ERK), SK1, and protein kinase C α (PKCα).

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0124136
Inhibition of Cancer Cell Growth by Exposure to a Specific Time-Varying Electromagnetic Field Involves T-Type Calcium Channels
Electromagnetic field (EMF) exposures affect many biological systems. The reproducibility of these effects is related to the intensity, duration, frequency, and pattern of the EMF. We have shown that exposure to a specific time-varying EMF can inhibit the growth of malignant cells. Thomas-EMF is a low-intensity, frequency-modulated (25-6 Hz) EMF pattern. Daily, 1 h, exposures to Thomas-EMF inhibited the growth of malignant cell lines including B16-BL6, MDA-MB-231, MCF-7, and HeLa cells but did not affect the growth of non-malignant cells. Thomas-EMF also inhibited B16-BL6 cell proliferation in vivo. B16-BL6 cells implanted in syngeneic C57b mice and exposed daily to Thomas-EMF produced smaller tumours than in sham-treated controls. In vitro studies showed that exposure of malignant cells to Thomas-EMF for > 15 min promoted Ca^{2+} influx which could be blocked by inhibitors of voltage-gated T-type Ca^{2+} channels. Blocking Ca^{2+} uptake also blocked Thomas-EMF-dependent inhibition of cell proliferation. Exposure to Thomas-EMF delayed cell cycle progression and altered cyclin expression consistent with the decrease in cell proliferation. Non-malignant cells did not show any EMF-dependent changes in Ca^{2+} influx or cell growth. These data confirm that exposure to a specific EMF pattern can affect cellular processes and that exposure to Thomas-EMF may provide a potential anti-cancer therapy.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9355252/
Pathological impact and medical applications of electromagnetic field on melanoma: A focused review 2022
Thomas-EMF
Thomas-EMF is an irregular frequency-modulated sequence that consists of a 3 millisecond (ms) waveform repeated at 25 Hz for the first 200 ms of presentation, followed by a gradual drop to 6 Hz for the last 500 ms. Thomas-EMF reduces cell growth while promoting calcium absorption.

https://pubmed.ncbi.nlm.nih.gov/26872872/
Calcium homeostasis and low-frequency magnetic and electric field exposure: A systematic review and meta-analysis of in vitro studies 2016
Low frequency magnetic field (LF MF) exposure is recurrently suggested to have the ability to induce health effects in society. Therefore, in vitro model systems are used to investigate biological effects of exposure. LF MF induced changes of the cellular calcium homeostasis are frequently hypothesised to be the possible target, but this hypothesis is both substantiated and rejected by numerous studies in literature. Despite the large amount of data, no systematic analysis of in vitro studies has been conducted to address the strength of evidence for an association between LF MF exposure and calcium homeostasis. Our systematic review, with inclusion of 42 studies, showed evidence for an association of LF MF with internal calcium concentrations and calcium oscillation patterns. The oscillation frequency increased, while the amplitude and the percentage of oscillating cells remained constant. The intracellular calcium concentration increased (SMD 0.351, 95% CI 0.126, 0.576). Subgroup analysis revealed heterogeneous effects associated with the exposure frequency, magnetic flux density and duration. Moreover, we found support for the presence of MF-sensitive cell types. Nevertheless, some of the included studies may introduce a great risk of bias as a result of uncontrolled or not reported exposure conditions, temperature ranges and ambient fields. In addition, mathematical calculations of the parasitic induced electric fields (IEFs) disclosed their association with increased intracellular calcium. Our results demonstrate that LF MF might influence the calcium homeostasis in cells in vitro, but the risk of bias and high heterogeneity (I(2)>75%) weakens the analyses. Therefore any potential clinical implications await further investigation.

https://pubmed.ncbi.nlm.nih.gov/33857627/
Necroptosis triggered by ROS accumulation and Ca^{2+} overload, partly explains the inflammatory responses and anti-cancer effects associated with 1Hz, 100 mT ELF-MF in vivo 2021
Whereas the anti-neoplastic activity of extremely low frequency magnetic fields (ELF-EMF) is well-documented in literature, little is known about its underlying anti-cancer mechanisms and induced types of cell death. Here, for the first time, we reported induction of necroptosis, a specific type of programed necrotic cell death, in MC4-L2 breast cancer cell lines following a 2 h/day exposure to a 100 Hz, 1 mT ELF-EMF for five days. For in vivo assessment, inbred BALB/c mice bearing established MC-4L2 tumors were exposed to 100 mT, 1 Hz ELF-EMF 2 h daily for a period of 28-day, following which tumors were dissected and fixed for evaluation of tumor biomarkers expression and types of cell death induced using TUNEL assay, Immunohistochemistry and H&E staining. Peripheral blood samples were also collected for assessing pro-inflammatory cytokine profile following exposure. An exaggerated proinflammatory response evident form enhancement of IFN-γ (4.8 ± 0.24 folds) and TNF-α (3.1 ± 0.19 folds) and number of tumors infiltrating lymphocytes (TILs), specially CD8+ Th cells (~20 folds), proposed occurrence of necroptosis in vivo. Meanwhile, exposure could effectively suppress tumor growth and expression of Ki-67, CD31, VEGFR2 and MMP-9. In vitro studies on ELF-EMF exposed MC-4L2 cells demonstrated a meaningful increase in phosphorylation of RIPK1/RIPK3/MLKL

proteins and cleavage of caspase-9/caspase-3, confirming occurrence of both necroptosis and apoptosis. Complementary in vitro studies by treating ELF-EMF exposed MC-4L2 cells with verapamil (a calcium channel inhibitor), N-acetyl cysteine (a ROS scavenger) or calcium chloride confirmed the role of elevated intracellular calcium and ROS levels in ELF-EMF induced necroptosis.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9939155/

Is extremely low frequency pulsed electromagnetic fields applicable to gliomas? A literature review of the underlying mechanisms and application of extremely low frequency pulsed electromagnetic fields 2023

Electromagnetic field is subdivided into pulsed EMF (PEMF) and continuous EMF, with the former being more advantageous than the latter because compared with continuous EMF, PEMF produces signals that could be perceived by brain more easily and delivers a large amount of energy in short bursts at a lower level of average energy. 13 , 14 Existing studies have revealed the potential of PEMF in treating depression, 15 , 16 osteoarthritis, 17 rheumatoid arthritis, 18 repairing tendons, 19 and preventing ulcer formation in diabetes patients. 20 Moreover, PEMF has been used to treat breast cancer 21 and melanoma. 22

However, PEMF has limited clinical use because its optimal parameters, such as frequencies, intensities, exposure times even waveforms, remain uncertain. For example, the frequency of PEMF is associated with its tissue penetrability and consequent biological effects, and PEMF has been found to be effective when its frequency ranges from 0.16 to 480 Hz and the intensity ranges from 0.6 to 250 mT. 23 In this review, we focus on extremely low-frequency PEMF(ELF-PEMF), a subdivision of PEMF with frequencies between 0 and 300 Hz, 24 which has the potential to penetrate the skull 10 , 25 and inhibit the growth of glioma cell lines. 26 , 27

The relationship between Ca2+ and gliomas began to draw attention 33 when T-type channels were found to be expressed in the proliferative stage of the cell cycle 34 and that the overexpression of T-type channels could induce the proliferation of glioma cells. 35 Blocking T-type channels Cav3.2, a target in gliomas, could reduce the survival rate of GBM cells and their resistance to temozolomide (TMZ). 36 Plus, calcium-activated potassium channels are found to be overexpressed in gliomas and are directly related to tumor growth and invasiveness. 37 However, ELF-PEMF appears to act differently because it activates the T-type calcium ion pathway, and has an impact on the membrane. During this process, Ca2+ ions are observed to move from the outside to the inside of cells via Ca2+ channels. The increase in calcium concentration under exposure to different ELF-PEMFs stems the growth of tumor cells, 22 , 27 , 38 which may involve different downstream signaling pathways.

https://pubmed.ncbi.nlm.nih.gov

Intracellular calcium oscillations induced in a T-cell line by a weak 50 Hz magnetic field. 1993

Applied weak magnetic fields have been shown to affect cellular activity on several levels, but the mechanisms involved remain elusive. We have decided to study an early signal transduction event in the human T cell line Jurkat; oscillations of free [Ca2+]i, of the type seen by crosslinking the CD3 complex. Cells were exposed to a 50 Hz, 0.1 mT, sinusoidal magnetic field while intracellular free calcium was measured in individual cells, using fura-2 as a probe. An acute response was observed with oscillatory increases in [Ca2+]i, which subsided when the field was turned off. The effect of the magnetic field on [Ca2+]i was comparable to that achieved by an anti-CD3 monoclonal antibody.

https://www.mdpi.com/1422-0067/25/5/2473

Pulsed Electromagnetic Fields (PEMFs) Trigger Cell Death and Senescence in Cancer Cells 2024

The currently available anti-cancer therapies, such as gamma-radiation and chemotherapeutic agents, induce cell death and cellular senescence not only in cancer cells but also in the adjacent normal tissue. New anti-tumor approaches focus on limiting the side effects on normal cells. In this frame, the potential anti-tumor properties of Pulsed Electromagnetic Fields (PEMFs) through the irradiation of breast cancer epithelial cells (MCF-7 and MDA-MB-231) and normal fibroblasts (FF95) were investigated. PEMFs had a frequency of 8 Hz, full-square wave type and magnetic flux density of 0.011 T and were applied twice daily for 5 days. The data collected showcase that PEMF application decreases the proliferation rate and viability of breast cancer cells while having the opposite effect on normal fibroblasts. Moreover, PEMF irradiation induces cell death and cellular senescence only in breast cancer cells without any effect in the non-cancerous cells. These findings suggest PEMF irradiation as a novel, non-invasive anti-cancer strategy that, when combined with senolytic drugs, may eliminate both cancer and the remaining senescent cells, while simultaneously avoiding the side effects of the current treatments.

Our findings are in accordance with a previous study that used the low-intensity, frequency-modulated (6–25 Hz) Thomas electromagnetic field (EMF) pattern [21]. The Thomas EMF was able to inhibit the growth of cancer cell lines including B16-BL6, MCF-7, MDA-MB-231 and HeLa via **increased Ca2+ uptake through T-type Ca2+ channels** but did not affect the growth of normal cells

In conclusion, PEMF irradiation is a promising pre-conditioning, non-invasive strategy for tumor elimination, limiting the side effects of traditional radiotherapy (Figure 6A), as revealed by our findings. PEMF-treated cancer cells not only displayed cell death but also senescence. In contrast, normal fibroblasts were not affected by the possible harmful effects of PEMFs, but increased their cellular viability (Figure 3C). These findings suggested that PEMFs reduced the viability of cancer cells without having side effects on the adjacent normal tissue (Figure 6B), an outcome that is observed during traditional radiation therapy. Finally, a two-step treatment consisting of PEMF irradiation followed by the targeted administration of a **senolytic** drug could alter the route of cancer therapeutics (Figure 6C).

https://pubmed.ncbi.nlm.nih.gov/20438704/

Magnetic fields at extremely low-frequency (50 Hz, 0.8 mT) can induce the uptake of intracellular calcium levels in osteoblasts 2010

Several studies have been undertaken to elucidate the effects of electromagnetic field (EMF) on intracellular calcium ([Ca(2+)](i)) in the past 20 years. However, still there were controversies of electromagnetic pollution within the scientific community. In this work, we studied the effects of alternative magnetic fields on intracellular calcium. Osteoblastic cells were used as a model both to test the hypothesis that extremely low-frequency (ELF) magnetic fields can alter the concentrations of the intracellular calcium, and to examine the 'window' effect predicted by our previous theoretical work. The outcome of this experiment demonstrated that 50 Hz, 0.8 mT magnetic field can induce the uptake of [Ca(2+)](i) in osteoblasts. The empirical evidences of the specified window effects of [Ca(2+)](i) in osteoblastic cells were reported for the first time in this work.

https://pubmed.ncbi.nlm.nih.gov/1854352/

Calcium uptake by leukemic and normal T-lymphocytes exposed to low frequency magnetic fields 1991
Calcium-ion uptake by normal and leukemia lymphocytes increased during a 30-min exposure to a 13.6 Hz, sinusoidal magnetic field at 20 microT peak. The time-varying field was horizontal and parallel to a 16.5 microT component of the ambient static magnetic field. The uptake of 45Ca2+ increased 102% in a line of murine, cytotoxic T-lymphocytes (C57B1/6-derived CTLL-1), increased 126% in freshly-isolated spleen lymphocytes (C57B1/6 mice), and increased 75% in a line of lymphoma cells (C57B1/6-derived EL4). In contrast, there was no effect when the same field was applied for 30 min immediately before--as opposed to during--incorporation of calcium ions. When spleen lymphocytes were exposed during incubation with 45Ca2+ to a 60 Hz magnetic field at 20 microT peak, a small but statistically significant increase (37%) in uptake of the labeled ions occurred. These results indicate that weak, alternating magnetic fields might affect calcium-dependent functions of normal and leukemic lymphocytes.

https://febs.onlinelibrary.wiley.com/doi/10.1016/0014-5793%2892%2981504-F
Pulsed magnetic field effects on calcium signaling in lymphocytes: Dependence on cell status and field intensity
The effect of 3-Hz, monopolar, quasi-rectangular magnetic field pulses on 45Ca2+ uptake in resting and mitogen-treated rat thymic lymphocytes was evaluated. A 30-min, non-thermal exposure to the pulsed magnetic field (B peak = 6.5 mT, E max = 0.69 mV/cm, J max = 2.6 μA/cm2) reduced Concanavalin A-induced 45Ca2+ uptake by 45%. It was observed that (i) the induction of the 3-Hz field response dependend on Ca2+ signal transduction activation; (ii) the response direction (stimulation or inhibition) depended on the level of lymphocyte mitogen responsiveness, and (iii) the field response magnitude increased with increasing magnetic field flux densities (B peak = 0, 1.6, 6.5 and 28 mT). Our results demonstrate field effects at B max nearly 104 greater than that of the average human environment for low-frequency magnetic fields and they are consistent with the independent results from other 3-Hz pulsed magnetic field studies with lymphocytes.

https://ieeexplore.ieee.org/document/4649613
Effects of magnetic fields on intracellular calcium oscillations 2008
It is shown that, the field frequency condition will influence the pattern of calcium oscillation while the field strength was given, and the magnetic field strength will change the pattern of calcium oscillation when the frequency was 50Hz and 100Hz. Therefore, intracellular calcium oscillations can be influenced by ELF magnetic fields and then a series cellular response could be transformed.

https://pubmed.ncbi.nlm.nih.gov/9952304/
Induction of intracellular calcium oscillations in human skin fibroblast populations by sinusoidal extremely low-frequency magnetic fields (20 Hz, 8 mT) is dependent on the differentiation state of the single cell 1999
Experiments were performed to analyze whether short-term exposure to a sinusoidal extremely low-frequency electromagnetic field (20 Hz, 8 mT) can alter the dynamics of intracellular calcium in diploid human skin fibroblasts. In heterogeneous fibroblast populations, about 30% of the cells responded with a change in the oscillation activity of intracellular calcium within 40 min. It was demonstrated at the level of the single cell that the responsiveness of fibroblast populations to extremely low-frequency electromagnetic fields depends on the specific differentiation state of the exposed cell. The data obtained clearly indicate that mitotic progenitor fibroblasts respond with an enhancement of the dynamics of calcium, whereas in postmitotic fibrocytes a reduction of the dynamics was observed when the cells were co-stimulated with suboptimal concentrations of platelet-derived growth factor. Thus data from our laboratory on terminal differentiation induced by extremely low-frequency electromagnetic fields may be correlated with changes in the dynamics of Ca2+ reported here.

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0167931
BEMER Electromagnetic Field Therapy Reduces Cancer Cell Radioresistance by Enhanced ROS Formation and Induced DNA Damage
A particular system is the BEMER therapy as a Physical Vascular Therapy for which a normalization of the microcirculation has been demonstrated by a low-frequency, pulsed EMF pattern. Open remains whether this EMF pattern impacts on cancer cell survival upon treatment with radiotherapy, chemotherapy and the molecular-targeted agent Cetuximab inhibiting the epidermal growth factor receptor. Using more physiological, three-dimensional, matrix-based cell culture models and cancer cell lines originating from lung, head and neck, colorectal and pancreas, we show significant changes in distinct intermediates of the glycolysis and tricarboxylic acid cycle pathways and enhanced cancer cell radiosensitization associated with increased DNA double strand break numbers and higher levels of reactive oxygen species upon BEMER treatment relative to controls. Intriguingly, exposure of cells to the BEMER EMF pattern failed to result in sensitization to chemotherapy and Cetuximab. Further studies are necessary to better understand the mechanisms underlying the cellular alterations induced by the BEMER EMF pattern and to clarify the application areas for human disease.

https://aacrjournals.org/cancerres/article/77/16/4389/623177/Normal-and-Malignant-Cells-Exhibit-Differentia
Normal and Malignant Cells Exhibit Differential Responses to Calcium Electroporation 2017
Necrosis was induced using calcium concentrations of 100–500 mmol/L and injection volumes 20%–80% of tumor volume. Notably, only limited effects were seen in normal tissue. Calcium content increased >7-fold in tumor and skin tissue after calcium electroporation but decreased in skin tissue 4 hours after treatment to levels comparable with untreated controls, whereas calcium content endured at high levels in tumor tissue. Overall, our results suggest that calcium electroporation can elicit a rapid and selective necrosis of solid tumors, with limited deleterious effects on surrounding normal tissues.
Intracellular free calcium (Ca2+) is a very important second messenger involved in numerous intracellular processes from fertilization through development, differentiation, and proliferation, to cell death (14, 15). Thus, cells have to chelate, compartmentalize, or extrude calcium to maintain homeostasis such that free intracellular calcium is sub-micromolar.

https://pubmed.ncbi.nlm.nih.gov/35929424/
Is extremely low frequency pulsed electromagnetic fields applicable to gliomas? A literature review of the underlying mechanisms and application of extremely low frequency pulsed electromagnetic fields 2023
Gliomas refer to a group of complicated human brain tumors with a low 5-year survival rate and limited therapeutic options. Extremely low-

frequency pulsed electromagnetic field (ELF-PEMF) is a specific magnetic field featuring almost no side effects. However, the application of ELF-PEMF in the treatment of gliomas is rare. This review summarizes five significant underlying mechanisms including **calcium ions**, autophagy, apoptosis, angiogenesis, and reactive oxygen species, and applications of ELF-PEMF in glioma treatment from a clinical practice perspective. In addition, the prospects of ELF-PEMF in combination with conventional therapy for the treatment of gliomas are reviewed. This review benefits any specialists, especially oncologists, interested in this new therapy because it can help treat patients with gliomas properly.