Iron – Magnetic Field Therapy

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Iron and magnetic: new research direction of the ferroptosis-based cancer therapy 2018

Ferroptosis is an iron depend cell death which caused by lipid peroxidation. Abnormal iron metabolism and high intracellular iron content are the characteristics of most cancer cells. Iron is a promoter of cell growth and proliferation. However, iron also could take part in Fenton reaction to produce reactive oxygen species (ROS). The intercellular ROS could induce lipid peroxidation, which is necessary for ferroptosis. Iron metabolism mainly includes three parts: iron uptake, storage and efflux. Therefore, iron metabolism-related genes could regulate intercellular iron content and status, which can be involved ferroptosis. In recent years, the application of nanoparticles in cancer therapy research has become more and more extensive. The iron-based nanoparticles (iron-based NPs) can release ferrous (Fe^{2+}) or ferric (Fe^{3+}) in acidic lysosomes and inducing ferroptosis. Magnetic field is widely used in the targeted concentration of iron-based NPs related disease therapy. Furthermore, multiple studies showed that magnetic fields can inhibit cancer cell proliferation by promoting intracellular ROS production. Herein, we focus on the relationship of between ferroptosis and iron metabolism in cancer cells, the application of nanoparticles and magnetic field in inducing ferroptosis of cancer cells, and trying to provide new ideas for cancer treatment research.

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The Role of Iron in Cancer Progression 2021

Iron is an essential trace element for the human body, and its deficiency or excess can induce a variety of biological processes. Plenty of evidences have shown that iron metabolism is closely related to the occurrence and development of tumors. In addition, iron plays an important role in cell death, which is very important for the development of potential strategies for tumor treatment.

However, although iron is essential for the normal physiological function of the human body, it may also be toxic in that it generates a large number of free radicals in the presence of hydrogen peroxide (7). For example, in the well-known Fenton reaction, ferrous iron (Fe^{2+}) reacts with hydrogen peroxide to be oxidized to ferric iron (Fe^{3+}) while generating hydroxyl radicals. When superoxide is present, the Fe^{3+} produced by the Fenton reaction can be reduced to Fe^{2+}, and then the Fenton reaction will proceed again, which called Haber-Weiss reaction (8). Both the Fenton reaction and Haber-Weiss reaction can produce a large number of hydroxyl radicals. Hydroxyl radical is one of the most important oxidant found in human body, which can lead to peroxidation and apoptosis by attacking protein, lipids, nucleic acids, and carbohydrates (9, 10).

Homeostasis of iron metabolism is a physiological process that needs to be strictly controlled. Iron is mainly present in the oxidized state (Fe^{3+}) and is divided into dietary iron and environmental iron. Dietary iron primarily exists as either nonheme bound iron or heme (11). Heme iron has a higher absorption rather than nonheme bound iron.

The excess iron is mainly stored in liver, which also acts as an iron-sensing organ and controls systemic iron through the secretion of the peptide hormone hepcidin (19).

A large number of studies have shown that abnormal iron homeostasis is one of the markers of cancer (Table 1). As the metabolism and proliferation rate of tumor cells are generally higher than that of normal cells, so their demand for iron is also significantly higher than that of normal cells, this leading to the exceeding oxidative stress; however, tumor cells can exert a concomitant upregulation of antioxidant defenses for survival, such as activating antioxidant transcription factors and promoting the expression of various antioxidant genes (57). Conversely, since tumor cells are strongly dependent on iron for their growth/proliferation, they are more sensitive to iron depletion than normal cells

Ferroptosis is caused by the redox imbalance between the production of oxidants and antioxidants, which is driven by the abnormal expression and activity of numerous redox active enzymes that produce or detoxify free radicals and lipid oxidation products (109, 111).

As the center of metabolism, mitochondria are an important source of ROS in most mammalian cells. Earlier studies showed that mitochondrial-mediated ROS production was not necessary for ferroptosis (108). However, recent studies have shown that mitochondrial-mediated ROS production, DNA stress, and metabolic reprogramming are necessary for lipid peroxidation and induction of ferroptosis (112–114).

Furthermore, studies also demonstrated that activating ferroptosis and apoptosis immensely increased chemotherapy sensitivity, which might provide strategies for the combination therapy for cancers.

Notably, many extracts from plants and herbs also exhibit anti-tumor effects by inducing ferroptosis. Z.X.Wang et al. found that **quercetin** could promote the degradation of lysosomal-dependent ferritin and the release of free iron, this effect and quercetin-induced ROS production synergistically led to lipid peroxidation and ferroptosis (142).

Many approaches have been constructed to treat cancer against intracellular iron metabolism disorders: one strategy is to deplete iron of tumor cells, such as iron chelator; another important one is to generate cytotoxic level of ROS or ferroptosis through excess iron in tumor cells (Table 3).

Elevated Iron Levels

The strategy in contrast to iron depletion is to supply cells with excess iron. Excess iron combines with high levels of unstable iron in tumor cells to produce large amounts of ROS to eliminate tumor cells. For example, the metal-containing drugs Ferrocene derivatives are stable and exhibit favorable redox properties, inhibiting proliferative activity of tumor cell lines (199). Additionally, Ferumoxytol is an iron oxide nanoparticle approved by the FDA for the treatment of clinical iron deficiency, and studies have shown that **ferumoxytol** can produce excessive amounts of free iron, the reactive oxygen species produced by which can cause cell death, increase oxidative stress, and reduce tumor burden cells in mouse leukemia models and patients (200).

What's more, **ascorbic acid therapy** is a variant of cancer treatment strategy by affecting the oxidation state of iron and increasing LIP levels, which is indicated for various tumors (201–203). Multiple clinical trials of this therapy are currently being pursued.

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LF-MF inhibits iron metabolism and suppresses lung cancer through activation of P53-miR-34a-E2F1/E2F3 pathway 2017

Iron (Fe) is an essential element for all living organisms. It is involved in several fundamental biological processed28. Accumulation of iron in

tissues increases the risk of cancer and TfR is frequently expressed multiple carcinoma cell lines29. The deficiency iron results in cell proliferation reduction and G1/S arrest of tumor cell. Depriving essential nutrient iron of cells by chelators has been used as an approach for cancer treatment30. Interestingly, previous study showed that LF-MF significantly changed iron concentration in liver and kidney31. However, to date it is not reported whether the interaction between iron and LF-MF may have an effect on cancer.
In this study, we found that LF-MF inhibited tumor growth in lewis lung cancer cells (LLC) mouse model. LF-MF also induced cell growth arrest and cell senescence in lung cancer cells. Specially, LF-MF enhanced the transcription of miR-34a and decreased the expression of E2F1/E2F3, which affect cell proliferation and cell senescence. We also confirmed that LF-MF suppresses the iron metabolism of lung cancer cells to stabilize p53 protein, which in turn enhance the transcription of miR-34a.
Biological effect of magnetic fields (MF) on tumor development has been widely investigated5, 6. Epidemiological studies suggest that increased childhood leukemia risk is associated with residential magnetic fields7. While, most animal studies results that combined MFs with known carcinogenic agents have produce equivocal results and have not provide evidence of the enhancement of carcinogenesis by MF exposure8, 9. In a toxicity pilot human study, patients with heavily pre-treated advanced cancer treated with different schedules of time exposure to LF-MF and no toxicity and adverse side effects were observed10. Of note, LF-MF, with property of the non-invasive, non-ionizing and non-thermal effects on cells and tissues, has been used to study the influence of various diseases, including cancer, pain, and spasticity reduction5, 11, 12. LF-MF inhibited cell growth and induced cell apoptosis and cell cycle arrest of prostate cancer mediated by ROS in vitro 13. Several in vivo studies proved the anti-tumor effects of LF-MF with decreased tumor volume and longer survival time14, 15. Meanwhile, a **15-mT and 50-Hz** LF-MF was introduced as a tumor necrosis agent16. A **5.5 mT and 50-Hz** LF-MF was showed to have synergistic activity with chemotherapy (cisplatin) against lung cancer in vivo 17. Interestingly, LF-MF induced germ cell apoptosis while had no effect on prenatal development18. In our previous studies, we examined the inhibitory effect of LF-MF with different parameters on gastric carcinoma cells and chose 7.5 Hz as the suitable frequency of LF-MF in our magnetic field exposure system19. We also found that the LF-MF (0.4T, 7.5 Hz) inhibited the growth of gastric cancer, hepatocellular carcinoma and melanoma cancer cells and improved immune function in tumor-bearing mice19,20,21,22. However, the detailed anti-tumor mechanisms of LF-MF still need to be clarified.

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LF-MF inhibits iron metabolism and suppresses lung cancer through activation of P53-miR-34a-E2F1/E2F3 pathway 2017
Our previous studies showed that low frequency magnetic fields (LF-MF) suppressed tumor growth and influenced the function of immune system. Nevertheless the mechanisms behind the effect of LF-MF still remain to be elucidated. In this study, Tumor- bearing mice subcutaneously inoculated with Lewis lung cancer cells were exposed to a LF-MF (**0.4T, 7.5 Hz**) for 35 days and Survival rate, tumor growth and the tumor markers were measured. Results showed that tumor growth was obviously inhibited with a prolonged survival of tumor- bearing mice by LF-MF exposure. In vitro experiments, LF-MF was found to induce cell growth arrest, cell senescence and inhibit iron metabolism of lung cancer cells

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Magnetic field boosted ferroptosis-like cell death and responsive MRI using hybrid vesicles for cancer immunotherapy 2020
We report a strategy to boost Fenton reaction triggered by an exogenous circularly polarized magnetic field (MF) to enhance ferroptosis-like cell-death mediated immune response, as well as endow a responsive MRI capability by using a hybrid core-shell vesicles (HCSVs). HCSVs are prepared by loading ascorbic acid (AA) in the core and poly(lactic-co-glycolic acid) shell incorporating iron oxide nanocubes (IONCs). MF triggers the release of AA, resulting in the increase of ferrous ions through the redox reaction between AA and IONCs. A significant tumor suppression is achieved by **Fenton** reaction-mediated ferroptosis-like cell-death. The oxidative stress induced by the Fenton reaction leads to the exposure of calreticulin on tumor cells, which leads to dendritic cells maturation and the infiltration of cytotoxic T lymphocytes in tumor. Furthermore, the depletion of ferric ions during treatment enables monitoring of the Fe reaction in MRI-R2* signal change. This strategy provides a perspective on ferroptosis-based immunotherapy.
Introduction
Chemotherapy and chemotherapy-based combination therapies have been developed and commonly performed for cancer treatment in clinics1. Due to the immune system contribution to the eradication of tumors, considerable attention has been given to developing chemotherapy-based immunotherapies2,3,4. Although the traditional strategy, apoptosis, is still widely used in chemotherapy for treating cancer, upcoming evidence shows its limitation for immunotherapy, such as inducing tumor resistance5, weakening co-stimulation of T cells, and even secreting immunosuppressive cytokines6. Compared with apoptosis, ferroptosis programmed cell death mechanisms, that is not dependent on apoptosis, have attracted excellent cancer research attention7,8. In the past few years, ferroptosis has been developed as a form of regulated cell death since it was first identified in an experimental context by applying the chemical inhibitor Erastin on cancer cells in 20129,10. So far, several signaling pathways of ferroptosis have been identified with cytological characteristics. The increase of intracellular Fe ions and follow-up Fenton reaction, which elevates reactive oxygen species (ROS) levels, lead to ferroptosis cell death by irresistible lipid peroxidation. The intense membrane lipid peroxidation and consequential loss of selective permeability of the plasma membrane are characterized in ferroptosis11,12. Another signaling pathway is involved with the inactivation of glutathione-dependent peroxidase 4, resulting in ferroptosis12,13,14. Generally, ferroptosis-induced cell death has been proved to be effective in killing cancer cells through ROS accumulation in cells15,16. Moreover, recent studies prove that the oxidative stress-inducing ferroptosis also upregulates the translocation of calreticulin (CRT) expression on the surface of tumor cells. The prophagocytic eat me CRT signal induces robust antitumor immune responses by eliciting phagocytosis of tumor-associated antigens2,17,18. The additional potential to trigger immune response is a promising feature of ferroptosis with the latest advances in immune cancer therapies.
Iron-based nanomaterials such as superparamagnetic iron oxide nanoparticles19, iron nanometallic glasses20, iron cross-linked gel nanoparticles21, and the iron-based metal−organic frameworks22 have been extensively tested as ferroptosis-inducing agents recently. Their capability of ROS generation through Fenton reaction of ferrous (Fe^{2+}) or ferric (Fe^{3+}) ions is believed to play a critical role in achieving a sufficient cancer therapeutic effect. Those iron-based nanomaterials improve the tumor specificity and therapeutic efficacy of ferroptosis cancer therapy to some degree. However, there are still some challenges, such as unwanted toxicity of carrier, low ROS conversion efficacy, required extra components for combinational effects, and a high dosage of nanomaterials that generally make it hard to be widely available.

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Electromagnetic fields regulate iron metabolism in living organisms: A review of effects and mechanism 2024

At present, a large number of data from whole organism and cellular level have demonstrated the effect of EMFs on iron metabolism. Its biological effects are complex and can't be classified into one category, which can be summarized as decrease, unchanged and increase. The reason for this phenomenon may be the difference of the observed object or the different parameters of EMFs, including MFD, gradient, direction, frequency and even exposure time.