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MAGNETIC HYPERTHERMIA CANCER TREATMENT

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Abstract :

Hyperthermia therapeutics (HT) is the uncovering of a region of the carcass to exalted hotness's to reach a therapeutic effect. HT anticancer characteristics and allure potential as a malignancy situation have been intentional for decades. Techniques used to reach a localized hyperthermic effect contain radiofrequency, ultrasound, cook, laser and drawing nanoparticles (MNPs). The use of MNPs for healing hyperthermia production is popular as magnetic hyperthermia remedy (MHT) and was first tried as a malignancy cure in 1957.

Keywords: Hyperthermia therapy (HT), radiofrequency, ultrasound, microwave, laser and magnetic nanoparticles (MNPs)., magnetic hyperthermia therapy (MHT), glioblastoma (GBM),

Introduction

Cancer is a significant public health issue worldwide, with a large number of cancer-related deaths (8.8 million in 2015 globally). It is currently responsible for the majority of deaths in the United States and Europe, second only to heart disease, and surpassing deaths from infectious diseases. Cancer can rapidly spread to other parts of the body through uncontrolled growth of cancer cells, leading to invasion of adjacent tissues, changes in cellular behavior, and immortality. Therefore, detecting cancer at an early stage is crucial for effective treatment. Various sensitive and selective bioassays, such as immunoassays, polymerase chain reaction, and fluorescence in situ hybridization, as well as imaging techniques such as magnetic resonance imaging, positron emission tomography, computed tomography, and ultrasound imaging, have been developed and are commonly used for cancer detection.
Conventional approaches for cancer treatment include surgical removal of the tumor, radiation therapy, chemotherapy, or a combination of these treatments. However, these therapies have limitations such as toxicity to healthy tissues, drug resistance of cancer cells, ineffectiveness against metastatic disease, difficulty in overcoming biological barriers, and cancer relapse. Therefore, new approaches that can complement or improve upon conventional therapies are urgently needed. Nowadays, various new methods using nanomaterials that exhibit reduced side effects, including photothermal therapy, DNA analysis, immunotherapy, photodynamic therapy, and magnetic hyperthermia, have been developed in the laboratory and are currently under clinical trials.
Magnetic fluid hyperthermia (MFH) is a promising non-invasive technique for cancer treatment and has several advantages compared to traditional hyperthermia therapy. This technique involves the selective administration of magnetic nanoparticles as a heat mediator into the tumor, followed by exposure of the tumor to an external alternating magnetic field. The heat inside the tumor increases due to the production of heat from internalized magnetic nanoparticles under the influence of audio and infrared alternating magnetic fields. Increased heat kills cancer cells through various mechanisms such as denaturation, encapsulation, and aggregation of proteins, apoptosis, necrosis, and coagulation, as well as indirect mechanisms mediated by stimulation of the immune system through overexpression of heat shock proteins. Magnetic hyperthermia has several benefits, including greater penetration of magnetic fields in tissues and enhanced targeting of magnetic nanoparticles to the tumor, compared to other hyperthermia methods.

Glioblastoma (GBM) is a highly aggressive form of brain tumor that is universally fatal. It is the most common primary brain malignancy in adults and the most aggressive according to the World Health Organization's classification (WHO Grade IV primary glioma) of brain tumors. GBM accounts for 12-15% of all brain tumors and has an incidence of 2-3 in 100,000 individuals. The standard of care for patients with GBM involves maximal surgical resection, when possible, followed by a combination of radiation therapy and chemotherapy. However, the prognosis for GBM patients remains poor, with a median survival time of 15 months. Magnetic hyperthermia is a promising new approach for GBM treatment that has shown encouraging results in preclinical studies. However, further research is needed to fully understand its potential for clinical use.

Macroscopic heating effects of MNPs

As one of ultimate fault-finding components in MNPs- MH, it is very inevitable for MNPs to be reliable and very adept. MNPs are magnetic nanomediators that intercede the adaptation of electromagnetic waves to thermal strength. As such, to advance the healing efficacy of MNPs-MH, ultimate fundamental action is to increase the warm change adeptness of MNPs. The inductive warming effect of MNPs, when endanger an AMF, can be afflicted by many determinants, such as hysteresis effect, entertainment effect, current current, domain divider, everyday reverberation, and so on 41. When the substance

and repetitiveness of AMF are insufficient to cause meaningful current current, visible thermal effectiveness of MNPs concede possibility be closely had connection with their inborn physicochemical possessions.

Magnetic loss of MNPs

The magnetic losses of magnetic nanoparticles (MNPs) refer to the amount of alternating magnetic field (AMF) energy that gets converted into heat during the process of magnetization reversal. These losses depend on factors such as the size and structure of the MNPs. When the size of MNPs decreases, their domain walls become more energy-intensive, leading to the formation of single-domain MNPs that exhibit superparamagnetic behavior at low intensities. The amount of heat generated by MNPs during each cycle of AMF depends on the extent of the hysteresis loop, which is affected by how quickly the magnetization follows the AMF changes. Superparamagnetic MNPs generate heat mainly due to the energy deficit resulting from the overcoming of the turning energy barrier under AMF.

To evaluate the magnetic heating efficiency of MNPs, various experimental techniques are used, such as calorimetry. This involves measuring the heat required to raise the temperature of the sample at a given rate, and using this information to calculate parameters such as the specific loss power (SLP) or intrinsic loss power (ILP). Calorimetry requires a systematic method of measuring temperature and a thermal model that accounts for the specific properties of the sample and its environment.

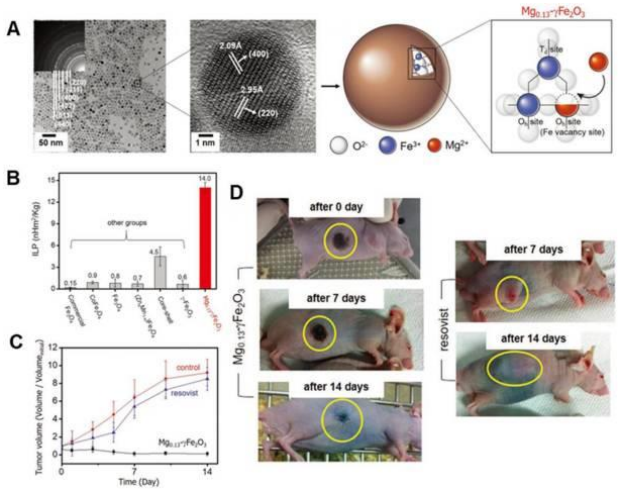
Another method of determining the SAR of MNPs is alternating current (AC) magnetometry, which involves measuring the changes in magnetic moment induced in a gradiometric inductive coil as the sample is exposed to an AMF. The SAR can be calculated from the area enclosed by the hysteresis loop of the magnetic material. This can be done using Equation (3), which relates SAR to the magnetic properties of the material

Infrared/Fluorescence thermometry

Color thermometry is commonly used for measuring temperature but can be affected by the angle between the surface and the camera. This makes it unreliable for intratumoral temperature measurement. Fluorescence thermometry can measure temperature at the nanoscale but is an indirect method that requires breaking a bond.

Strategies for improving SAR

Improving the Specific Absorption Rate (SAR) of magnetic nanoparticles (MNPs) is crucial for their biomedical applications. Researchers have found that the SAR can vary significantly depending on the type of MNPs used, their magnetic properties, and the magnetic field strength. To enhance the SAR, scientists are exploring ways to select appropriate materials, control particle size, composition, shape, and surface structure. MNPs with higher magnetic exposure and Ms are desirable for better SAR. Additionally, the SAR value is directly proportional to Ms but inversely proportional to the size of MNPs. Therefore, MNPs with high Ms and mono-dispersivity are ideal for biomedical applications. The use of Combidex and Mg0.13-γFe2O3 nanofluids has shown promising results in improving SAR for in vivo experiments.



Composition and shape effect of MNPs on SAR.

The various ways researchers have attempted to optimize magnetic nanoparticles (MNPs) for magnetic hyperthermia (MH) applications. Some of the techniques mentioned include exchange-coupling, which can adjust the drawing characteristics of MNPs and enhance their magnetic loss. The shape of the particles is also important for obtaining high specific absorption rates (SAR), and different morphologies have been studied, such as chain-like magnetotactic microorganisms and nanodisc-shape MNPs. Additionally, researchers have investigated the magnetic properties of cubic and ring-shaped MNPs and ferrimagnetic vortex-rule nanorings (FVIOs). The FVIOs have been found to have an extremely high SAR advantage and have shown

promising results in in vivo anti-carcinoma experiments. Overall, it seems that researchers are trying to optimize the magnetic properties of MNPs for use in MH therapy.

Samples	Shape	Size (nm)	M_s(emu/g)	F (kHz)	*H* (kA/m)	SAR/SLP (W/g)	ILP (nHm^2/kg)	Ref.
$Mg_{0.13}$@γ-Fe_2O_3	sphere	7		110	11.14	191	14	25
$Fe_{0.6}Mn_{0.4}O$	nanoflowers	102.7	6	366	32	535	1.45	21
$Ni_{0.8-x}Zn_{0.2}Mg_xFe_2O_4$ (x=0)	sphere	36	43.1			-		65
$Zn_{0.4}Mn0_{.6}Fe_2O_4$	sphere	15	175	500	3.7	432	63	22
Fe_3O_4	sphere	22	65	500	15.5	716	5.96	23
$MnFe_2O_4$@$CoFe_2O_4$	core@shell	15	100	500	37.3	3034	4.36	20
$CoFe_2O_4$@$Ni_{0.5}Zn_{0.5}Fe_2O_4$		9	28.2	265	30	25	0.10	67
Fe@Fe_3O_4		13	164	170	26.4	140	1.18	63
FePt@Fe_3O_4		15	36	630	18.8	1120	5.03	68
magnetosomes	chains	45.5	81	470	14.4	600	6.16	69
magnetosomes	chains	-	70	108	70.4	1242	2.32	70
magnetosomes	chains	30	-	410	10	960	23.4	30
magnetosomes	chains	40		198	15.2	40	0.87	71
magnetosomes	chains	35	61.4	750	5	171	9.12	72
magnetosomes	chains	45		75	30	375	5.56	74
Shape regulation								
Samples	**Shape**	**Size (nm)**	**M_s(emu/g)**	**F (kHz)**	***H* (kA/m)**	**SAR/SLP (W/g)**	**ILP (nHm^2/kg)**	**Ref.**
$Zn_{0.4}Fe_{2.6}O_4$	spheres	22	145			-		28
	cubes	18	165	500	37.4	1860	2.66	
Fe_3O_4	nanodiscs	125	435	488	47.8	5000	4.48	29
Fe_3O_4	nanorings	70	-	400	59.2	3050	2.18	31
$CoFe_2O_4$@$Zn_{0.4}Fe_{2.6}O_4$	core@shell	60	190	500	37.4	10600	15.16	20

current loss

Leaders in alternating magnetic fields generate current through movement or field intensity changes. Magnetic nanoparticles have been known to generate heat in AMF. Non-magnetic materials like gold nanoparticles and hypertonic saline also show thermal effects under AMF. This offers new research opportunities for magnetothermal cancer therapy.

Effects of local induction heat

Extensive research has met on the visible volume. Recent surveys have submitted that the heat generated by a alone MNP maybe highly local at nanometer ranges inside the encircling environment of MNP 37. This local-thermia maybe employed as an incentive determinant to manage cell function/intracellular parts, that can contribute to tumor container death. In 1979, Gordon and others. 36 manifested a more effective container apoptosis/fatality encouraging effect with internalized MNPs on account of the protected cell sheet, that enhanced the warm effect. Sanz and others. 38 stated MNPs-MH enhanced container toxicity concerning exogenous warming, that fully confirmed that intracellular hyperthermia is attainable. introductory heating belongings of many homogeneously scattered MNP throughout a It has existed earlier reported that the local warming happens forthcoming the surface of MNPs can induce organic belongings and regulate the physiologic and biochemical features of certain particles, and so inducing functional changes in all animal. Huang and colleagues illustrated that MNPs intend the outer container sheath manage activate ions channels accompanying a very pertaining to a focus temperature increase outside thermally moving the Golgi apparatus 34. It is well authorized that Fe3O4 nanoparticles are simple Fenton nanoagents that can generate ROS 86, and therefore smart to induce swelling container apoptosis. It is noteworthy that the alive MIONs under AMF can deepen the ROS era in tumor microenvironments (TME), superior to an embellished therapeutic effect 87. Clerc and others. 39 secondhand magnetic following a time-lysosomal hyperthermia (MILH) to explain that container death through a non-apoptotic indicating road can be generated by utilizing Gastrin-grafted MNPs specifically brought to lysosomes of the cyst containers (Figure (Figure6b).6b). The cell passing was assign to the local temperature increase at the outskirts of the MNPs that enhances the ROS result through lysosomal Fenton backlash. After that, MILH induces lipid peroxidation, lysosomal membrane permeabilization, and discharge of lysosomal enzymes into the cytosol, containing Cathepsin-B which activates Caspase-1 but not apoptotic Caspase-3. This work elucidated the basic and microscopic mechanisms complicated in malignancy container death persuaded by MILH.

MNPs-MH therapy-based synergistic strategy

In addition to generally utilizing MNPs-MH therapy to cancel the swelling cells by way of introductory heating, it maybe secondhand as an adjuvant situation to dispassionate radiotherapy and chemotherapy, in addition to expected used in collaboration accompanying immunotherapy, and photothermal/PDT et al. It has excellent importance in reducing allure toxicity and reactions, accordingly improving the forecast of cases. In addition to a cumulative effect, a much in vogue syngersim maybe achieved for one shared enhancement effect of the individual cytotoxic means of each game plan on each other.

MNPs-MH combined with chemotherapy

Magnetic iron oxide nanoparticles (MIONs) can be utilized for targeted drug delivery, controlled drug release under an external field, and as a prompt for magnetic field-mediated hyperthermia (MH) as a cancer treatment. Studies have shown that MIONs-MH can induce vasodilation, increase drug delivery and release, enhance drug cytotoxicity, and disrupt tumor DNA repair mechanisms and drug resistance. MIONs-MH also improves drug intracellular uptake by changing the permeability of the cell membrane. Recent research has demonstrated that controlled radio frequency fields can be used to generate localized heat using MIONs, providing a more precise treatment approach. This technique has also shown promise in temporarily opening the blood-brain barrier when treating brain tumors.

MNPs-MH combined with radiotherapy

Since the finding of X-beams by Roentgen, radiation healing (RT) has existed imitated as a standard treatment approach for malignancy. However, the therapeutic effect is regularly concealed by allure side effects confronted for one usual tissue and the fallout fighting induced by hypoxia. MH plays a important act while radiosensitization, which can embellish the damage to the lump containers and blood ships by obstruct the repair mechanism of lump DNA following in position or time their harm. It has been manifested that the mixture of MNPs-MH and RT not only can efficiently kill opposing containers and lower toxicity to rational tissue, it can still lower the fallout dosage 103, 104. Jiang and others. 105 planned a gadolinium-drugged iron oxide nanoparticles (GdIONP) accompanying bigger SAR, and they surveyed its healing belongings when used in the combinational wireless-thermotherapy. The results marked that the efficacy of RT maybe reinforced accompanying GdIONP-mediated hyperthermia in two habits; (1) by lowering the fraction of hypoxic containers that help dissemination resistance and, (2) by encouraging lump-distinguishing localized vascular division and fatality. Due to the trouble of external strength beginnings in reaching the goals to create able heat, significant benefits of thermo-radiotherapy can be restricted to detail tumors 106. Nevertheless, MH can also be a part of an secondary treatment to radiotherapy for metastatic conscience tumor. Wang and others. 107 revealed a three cooperative conduct by MH that happened in a tremendous bettering in body part metastasis and in overall endurance of rodent under combinational MH/RT treatment; (1) advancing the antagonistic-cyst efficiency of radiotherapy through Bax-interfered container death, (2) reconstructing natural exemption which is restrained under radiotherapy, and (3) diminishing the potential of radiotherapy to embellish MMP-9 expression.

MNPs-MH combined with immunotherapy

In addition to the murder of malignancy cells accompanying heat, MNPs-MH can likewise trigger an antagonistic-cyst invulnerable response by dropping cyst antigens and endogenous something which incites activity (for example, heat shock proteins and damage-befriended molecular patterns), that shows significant potential for Cancer analysis (exceptionally for metastatic tumors) 109-111. In 1998, Kobayashi et al. completed activity an experiment by which the left side of the Cancer was commit MNPs-MH situation mediated by magnetite liposomes. By transplanting right-9 informer glioma tumor model into each leg part of a informer, the remote tumor more revealed inhibited progress even outside bear hardship hyperthermia. It was revealed that CD3+, CD4+, CD8+, and NK containers were discovered in both the abandoned and right Cancer tissues of the rats, that lead to enduring and T-9 container-particular acquired exemption 112.

MNPs-MH combined with PTT or PDT

MNPs-MH has limitations in clinical applications, such as the need for high MNPs concentration and reduced warming efficiency in cellular environments. Direct intratumoral injection is also required due to the low warming efficiency of MNPs. NPTT is another nanotechnology for tumor treatment, but it has drawbacks such as excessive light exposure and a decline in light force. Combining MNPs-MH and NPTT can enhance the heat effect and achieve a synergistic effect. Researchers have developed multifunctional nanoprobes that can achieve in vivo photo-induced hyperthermia. Biocompatible Fe3O4-Pd Janus NPs have also been created to attain higher photo-induced heating efficiency and enhance tumor inhibition in animal models.

MNPs-MH combined with gene therapy

Hyperthermia, a local heat treatment, is an effective approach to induce death in tumor cells. Heat-shock proteins (HSPs) play a crucial role in protecting cells from thermal stress and other stress factors. Manipulating the expression of HSPs through genetic editing can improve the efficiency of gene therapy. Stem cell-based gene therapy has potential for cancer treatment but can have side effects. A study delivered a heat-inducible DNA therapy using nanoparticles to mesenchymal stem cells, which selectively expressed a tumor necrosis factor that induced apoptosis in ovarian tumor cells. Magnetic nanoparticles (MNPs) can be used to deliver drugs and genes, and also create heat under AMF exposure, making them useful for hyperthermia-based self-murder DNA therapy in hepatocellular carcinoma.

Imaging-assisted targeted MNPs-MH

MNPs have a significant role in MRI applications for diagnostic radiology. Engineered MNPs can enhance MRI contrast and induce local hyperthermia through AMF energy. However, collateral heat damage to healthy tissue is a concern in using MNPs-MH for cancer treatment. To address this issue, a specific strategy is needed for more precise targeting of cancerous tissue. Thorat et al. developed a functionalized superparamagnetic nanocomposite with an anticancer drug that can be used for MRI-guided MNPs-MH and chemotherapy. The nanocomposites induced hyperthermia that resulted in up to 80% tumor cell death within 30 minutes under artificial conditions.

Clinical Trials of MNPs-MH

MNPs-based therapy for cancer treatment has gained significant interest due to its potential therapeutic benefits. One such therapy is the NanoTherm® healing, which is the world's first MNP-based therapy for prostate and brain tumors. The therapy has undergone preclinical and clinical trials, and its effectiveness is being evaluated in several ongoing clinical trials. The first clinical trial of MNPs-MH therapy was conducted in 2003 on 14 patients with glioblastoma multiforme, which demonstrated the feasibility and efficacy of the therapy. Following the success of the phase I trial, a phase II trial was initiated, and the efficacy of the therapy is still being evaluated. In 2013, MagForce AG initiated a post-market clinical trial for the treatment of recurrent glioblastoma with NanoTherm® therapy. Recently, the therapy has also shown promising results in the treatment of middle-risk prostate cancer.

Challenges and Perspectives

In this review, the current up-to-date designs for reconstructing the therapeutic productiveness of MNPs-MH are argued. Significant consideration has happened attracted on the use of MNPs to raise the temperature of carcinoma fabric to the hyperthermia range in consideration of allow tumor medicine. The capability to harmony the amount, arrangement, and study of plants of MNPs admits the optimization of MNPs. Ultimately, this leads to enough and persuasive warming characteristics, that is considered as a direct habit of reconstructing healing efficiency. The current experimental evidence from research supports the idea that MNPs maybe devised to cause local warm belongings. A deep understanding of this local heat superior to the division of basic makeups and cell extinction outside the need for a visible hotness increase further supports the efficiency of MNPs in the therapy. By synergistically joining MNPs-MH accompanying added healing plans, such as a destructive agent, radiotherapy, immunotherapy, and photothermal/PDT, it admits further augmentation of the influence of the antitumor situation. Despite the current tremendous progress in MNPs-MH 53, various staying challenges need expected overcome.

CONCLUSION

1. In magnetic hyperthermia experiments, an alternating magnetic field is applied to the nanoparticle sample and the variation of temperature is measured with respect to time and graphs were plotted.
2. As the time increases, temperature was also increased linearly. But at low frequencies, temperature increase was not enough for
    a. hyperthermia treatment. We need the frequency above 500 KHz to
    b. increase the temperature 2 degrees per minute

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