Magnetic Hyperthermia for Cancer Treatment: Synthesis of Nanoparticles for Thermo-Chemotherapy

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Abstract- **Hyperthermia therapy is a type of medical treatment in which body tissue is exposed to higher temperatures in an effort to treat Lyme disease and cancer.[1]**

Hyperthermia uses higher temperatures than diathermy, which is the deep heating of body tissue for relaxation or physical therapy. Techniques that bring local tissues to quite high temperatures, such as radio frequency ablation, are also not usually included in "hyperthermia".[2] When combined with radiation therapy, it is called thermo radiotherapy.

Hyperthermia is defined as supra-normal body temperatures. There is no consensus as to what is the safest or most effective target temperature for the whole body. During treatment the body temperature reaches a level between 39.5 and 40.5 °C (103.1 and 104.9 °F).[3] However, other researchers define hyperthermia between 41.8–42 °C (107.2–107.6 °F) (Europe, USA) to near 43–44 °C (109–111 °F) (Japan, Russia).[4]

Index terms- **Magnetic nanoparticle, hyperthermia, cancer, tumor**

INTRODUCTION

Heat in the Ancient Times The use of high temperature as a method of treatment of various diseases (including cancer) was common in various cultures since ancient times. Primarily, the heat had sacral meaning and was associated with the healing power of the Sun [16]. Therefore, it was used for the treatment of locally affected human body parts or the whole organism. For that purpose, hot water and sand (mud baths) from natural thermal springs, and hot air and steam occurring in the volcanic caves were utilize Local hyperthermia heats a very small area and is typically used for cancers near or on the skin or near natural openings in the body (e.g., the mouth).[5] In some instances, the goal is to kill the tumor by heating it, without damaging anything else. The heat may be created with microwave, radiofrequency, ultrasound energy or using magnetic hyperthermia (also known as magnetic fluid hyperthermia)[6][7][8]). Depending on the location of the tumor, the heat may be applied to the surface of the body, inside normal body cavities, or deep in tissue through the use of needles or probes. One relatively common type is radiofrequency ablation of small tumors.[9] This is easiest to achieve when the tumor is on a superficial part of the body, which is called superficial hyperthermia, or when needles or probes are inserted directly into the tumor, which is called interstitial hyperthermia.

Regional hyperthermia heats a larger part of the body, such as an entire organ or limb. Usually, the goal is to weaken cancer cells so that they are more likely to be killed by radiation and chemotherapeutic medications. This may use the same techniques as local hyperthermia treatment, or it may rely on blood perfusion.[5] In blood perfusion, the patient's blood is removed from the body, heated up, and returned to blood vessels that lead directly through the desired body part. Normally, chemotherapy drugs are infused at the same time. One specialized type of this approach is continuous hyperthermic peritoneal perfusion (CHPP), which is used to treat difficult cancers within the peritoneal cavity (the abdomen), including primary peritoneal mesothelioma and stomach cancer. Hot chemotherapy drugs are pumped

directly into the peritoneal cavity to kill the cancer cells.[9]

TREATMENTS

The St. George Klinik for hyperthermia in Germany is using it to kill Lyme disease bacteria that spread throughout the whole body. The entire body including blood is heated for approximately 2 hours.

It is hypothesized that hyperthermia may be able to decrease the size of cancers.[1] Research is ongoing.[1]Localized hyperthermia treatment is a well-established cancer treatment method with a simple basic principle: If a temperature elevation to 104ºF can be maintained for one hour within a cancer tumor, the cancer cells will be destroyed.[10]The schedule for treatments has varied between study centers. After being heated, cells develop resistance to heat, which persists for about three days and reduces the likelihood that they will die from direct effects of the heat.[11] Some even suggest maximum treatment schedule of twice a week.[12] Japanese researchers treated people with "cycles" up to four times a week apart.[13] Radio sensitivity may be achieved with hyperthermia, and using heat with every radiation treatment may drive the treatment schedule.[11] Moderate hyperthermia treatments usually maintain the temperature for approximately an hour.[12]

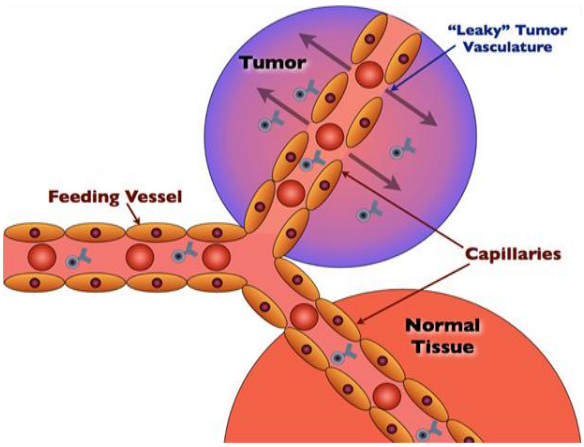
Hyperthermia treatment is a non-invasive method of increasing tumor temperature to stimulate blood flow, increase oxygenation and render tumor cells more sensitive to radiation. By adding hyperthermia to radiation therapy, radiation oncologists can increase tumor control while minimizing damage to healthy tissue.

Hyperthermia helps address the limitations of radiation for many patients by effectively increasing the radiation dose without increasing in unwanted side effects.

ENHANCED PERMEABILITY AND RETENTION (EPR) EFFECT

For a tumor to grow beyond approximately two millimeters in diameter, tumor cells must excrete a variety of molecular signalers to initiate blood vessel growth and recruit nutrients.107 The growth of new blood vessels is termed “neovascularization” or “angiogenesis”. Tumoral angiogenesis typically is disorganized, occurring rapidly. This type of vascularization results in large (600–800 nm) fenestrations (gaps) between adjacent tumor endothelial cells.108 These fenestrations permit substances injected into the blood — for instance, gadolinium contrast used to increase signal within tumor tissues during MRI imaging — to accumulate within tumors, even without any targeting moiety present.109 By injecting nanoparticles systemically, it is hoped that a large percentage of the injected dose will accumulate within tumors due to the EPR effect. The EPR (enhanced permeability and retention) effect allows for preferential diffusion of substances present in the blood into tumors (as shown with the schematic of targeted nanoparticles in this figure).

Nanoparticle size and surface characteristics will affect their tumor localization and overall bio distribution in vivo. As noted, nanoparticles over 100 nm in diameter and particles with more hydrophobic coatings will be rapidly depleted from circulation through RES filtration.100 Smaller particles are therefore more desirable from a distribution standpoint as well as for penetration and diffusion by the EPR effect. Nanoparticles of decreasing size, however, have higher surface area to volume ratios which favors plasma protein adherence. With significant protein agglomeration, the



particles will again be recognized and cleared by reticuloendothelial macrophages.115 Since surface coatings, along with targeting moiety attachment, to the nanoparticle will determine the final hydrodynamic diameter, the ability to decrease surface thickness while ensuring stability and maintaining sizeable crystal cores is invaluable.

ADVERSE EFFECTS

External application of heat may cause surface burns.[12] Tissue damage to a target organ with a regional treatment will vary with what tissue is heated (e.g. brain treated directly may injure the brain, lung tissue treated directly may cause pulmonary problems) Whole body hyperthermia can cause swelling, blood clots, and bleeding.[11] Systemic shock, may result, but is highly dependent upon method difference in achieving it. It may also cause cardiovascular toxicity.[9] All techniques are often combined with radiation or chemotherapy, muddying how much toxicity is the result of those treatments versus the temperature elevation achieved.

Are there any side effects?

Side effects may include skin discomfort or local pain. Hyperthermia can also cause blisters and sometimes burns, but generally these heal quickly. Local hyperthermia can cause pain at the site, infection, blood clots, burns, and damage to the muscles, skin, and nerves in the treated area. Whole body hyperthermia can cause diarrhea, nausea, and vomiting. Please note that improved technology, research, and treatment experience have resulted in fewer side effects. Most side effects people experience are short-term and not serious.

MECHANISM

Hyperthermia can kill cells directly, but its more important use is in combination with other treatments for cancer.[11] Hyperthermia increases blood flow to the warmed area, perhaps doubling perfusion in tumors, while increasing perfusion in normal tissue by ten times or even more.[11] This enhances the delivery of medications. Hyperthermia also increases oxygen delivery to the area, which may make radiation more likely to damage and kill cells, as well as preventing cells from repairing the damage induced during the radiation session.[12]

Cancerous cells are not inherently more susceptible to the effects of heat.[11] When compared in in vitro studies, normal cells and cancer cells show the same responses to heat. However, the vascular disorganization of a solid tumor results in an unfavorable microenvironment inside tumors. Consequently, the tumor cells are already stressed by low oxygen, higher than normal acid concentrations, and insufficient nutrients, and are thus significantly less able to tolerate the added stress of heat than a healthy cell in normal tissue.[11]

Mild hyperthermia, which provides temperatures equal to that of a naturally high fever, may stimulate natural immunological attacks against the tumor. However it is also induces a natural physiological response called thermo tolerance, which tends to protect the treated tumor.[11]

Moderate hyperthermia, which heats cells in the range of 40 to 42 °C (104 to 108 °F), damages cells directly, in addition to making the cells radiosensitive and increasing the pore size to improve delivery of large-molecule chemotherapeutic and immunotherapeutic agents (molecular weight greater than 1,000 Daltons), such as monoclonal antibodies and liposome-encapsulated drugs.[11] Cellular uptake of certain small molecule drugs is also increased.[11]Very high temperatures, above 50 °C (122 °F), are used for ablation (direct destruction) of some tumors.[12] This generally involves inserting a metal tube directly into the tumor, and heating the tip until the tissue next to the tube has been killed.

FUTURE DIRECTIONS

Hyperthermia may be combined with gene therapy, particularly using the heat shock protein 70 promoter.[11]

Two major technological challenges make hyperthermia therapy complicated: the ability to achieve a uniform temperature in a tumor, and the ability to precisely monitor the temperatures of both the tumor and the surrounding tissue.[11] Advances in devices to deliver uniform levels of the precise amount of heat desired, and devices to measure the total dose of heat received, are hoped for.[11]

In locally advanced adenocarcinoma of middle and lower rectum, regional hyperthermia added to chemo radio therapy achieved good results in terms of rate of sphincter sparing surgery.[18]

MAGNETIC HYPERTHERMIA

Magnetic hyperthermia is an experimental treatment for cancer, based on the fact that magnetic nanoparticles can transform electromagnetic energy from an external high-frequency field to heat[19]. This is due to the magnetic hysteresis of the material when it is subjected to an alternating magnetic field.

The area enclosed by the hysteresis loop represents losses, which are commonly dissipated as thermal energy [19]. In many industrial applications this heat is undesirable, however it is the basis for magnetic hyperthermia treatment.[citation needed]

CO-PRECIPITATION

Main article: Co-precipitation

Co-precipitation is a facile and convenient way to synthesize iron oxides (either Fe3O4 or γ-Fe2O3) from aqueous Fe2+/Fe3+ salt solutions by the addition of a base under inert atmosphere at room temperature or at elevated temperature. The size, shape, and composition of the magnetic nanoparticles very much depends on the type of salts used (e.g.chlorides, sulfates, nitrates), the Fe2+/Fe3+ ratio, the reaction temperature, the pH value a

And ionic strength of the media,[21] and the mixing rate with the base solution used to provoke the precipitation.[31] The co-precipitation approach has been used extensively to produce ferrite nanoparticles of controlled sizes and magnetic properties.

THERMAL DECOMPOSITION

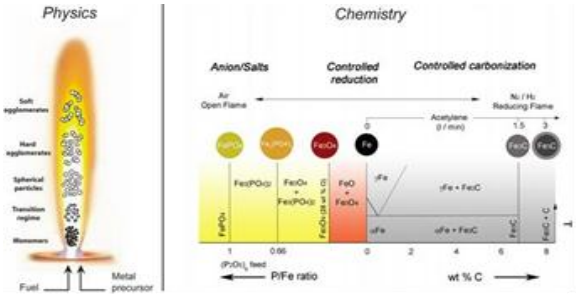
Main article: Thermal decomposition

Magnetic nanocrystals with smaller size can essentially be synthesized through the thermal decomposition of alkaline organometallic compounds in high-boiling organic solvents containing stabilizing surfactants.[21][39][40]

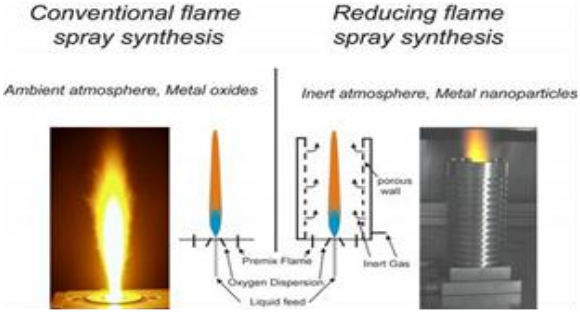
MICROEMULSION

Main article: Microemulsion

Using the microemulsion technique, metallic cobalt, cobalt/platinum alloys, and gold-coated cobalt/platinum nanoparticles have been synthesized in reverse micelles of cetyltrimethly ammonium



Octane as the oil phase.,[21][41]



bromide, using 1-butanol as the cosurfactant and

FLAME SPRAY SYNTHESIS

Using flame spray pyrolysis [30][42] and varying the reaction conditions, oxides, metal or carbon coated nanoparticles are produced at a rate of > 30 g/h .

Various flame spray conditions and their impact on the resulting nanoparticles

TYPES OF MAGNETIC NANOPARTICLES

Oxides: ferrites

Ferrite nanoparticles or iron oxide nanoparticles (iron oxides in crystal structure of maghemite or magnetite) are the most explored magnetic nanoparticles up to date. Once the ferrite particles become smaller than 128 nm[22] they become super paramagnetic which prevents self-agglomeration since they exhibit their magnetic behavior only when an external magnetic field is applied. The magnetic moment of ferrite nanoparticles can be greatly increased by controlled clustering of a number of individual super paramagnetic nanoparticles into super paramagnetic nanoparticle clusters, namely magnetic nanobeads.[1] With the external magnetic field switched off, the remanence falls back to zero. Just like non-magnetic oxide nanoparticles, the surface of ferrite nanoparticles is often modified by surfactants, silica,[1] silicones or phosphoric acid derivatives to increase their stability in solution.[23]

Maghemite nanoparticle cluster with silica shell.

TEM image of a maghemite magnetic nanoparticle cluster with silica shell.[3][24]

FERRITES WITH A SHELL

The surface of a maghemite or magnetite magnetic nanoparticle is relatively inert and does not usually

allow strong covalent bonds with functionalization molecules. However, the reactivity of the magnetic nanoparticles can be improved by coating a layer of silica onto their surface.[25] The silica shell can be easily modified with various surface functional groups via covalent bonds between organo-silane molecules and silica shell.[26] In addition, some fluorescent dye molecules can be covalently bonded to the functionalized silica shell.

Nanoparticle clusters with narrow size distribution consisting of super paramagnetic oxide nanoparticles (~ 80 maghemite super paramagnetic nanoparticles per bead) coated with a silica shell have several advantages over metallic nanoparticles:[1]

Higher chemical stability (crucial for biomedical applications)

Narrow size distribution (crucial for biomedical applications)

Higher colloidal stability since they do not magnetically agglomerate

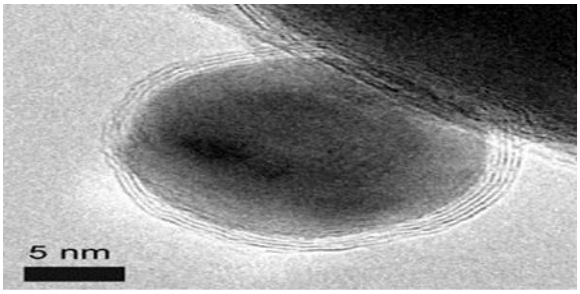
Magnetic moment can be tuned with the nanoparticle cluster size

Retained super paramagnetic properties (independent of the nanoparticle cluster size)

Silica surface enables straightforward covalent functionalization

METALLIC

Metallic nanoparticles may be beneficial for some technical applications due to their higher magnetic moment whereas oxides (maghemite, magnetite) would be beneficial for biomedical applications. This also implies that for the same moment, metallic nanoparticles can be made smaller than their oxide counterparts. On the other hand, metallic nanoparticles have the great disadvantage of being pyrophoric and reactive to oxidizing agents to various degrees. This makes their handling difficult and enables unwanted side reactions which makes them less appropriate for biomedical applications



Colloid formation for metallic particles is also much more challenging. Cobalt nanoparticle with graphene shell. Cobalt nanoparticle with graphene shell (note: The individual graphene layers are visible)[28]

METALLIC WITH A SHELL

The metallic core of magnetic nanoparticles may be passivated by gentle oxidation, surfactants, polymers and precious metals.[21] In an oxygen environment, Co nanoparticles form an anti-ferromagnetic CoO layer on the surface of the Co nanoparticle. Recently, work has explored the synthesis and exchange bias effect in these Co core CoO shell nanoparticles with a gold outer shell.[29] Nanoparticles with a magnetic core consisting either of elementary Iron or Cobalt with a nonreactive shell made of graphene have been synthesized recently.[30] The advantages compared to ferrite or elemental nanoparticles are:

HIGHER MAGNETIZATION

Higher stability in acidic and basic solution as well as organic solvents Chemistry[28] on the graphene surface via methods already known for carbon nanotubes

CONCLUSION

Requirements for Magnetic Nanoparticles Used in Cancer Therapy

Producing localized hyperthermia of malignant lesions, using nanoparticles and AMF, has the potential to either directly kill the cancer cells or enhance susceptibility to radiation or chemotherapy. Several critical developments are needed to make nanoparticle-based hyperthermia clinically viable:

The nanoparticles need to be coated for bio-compatibility, low toxicity and evasion of the RES and kidney filtration.

Nanoparticles in tumors must be selectively heated via focused AMF, leaving nanoparticles that collect in potentially vulnerable regions (liver, kidney) unheated.

REFERENCE

[1] "Hyperthermia in Cancer Treatment". National Cancer Institute. 9 September 2011. Retrieved 7 November 2017.

[2] This article incorporates public domain material from the U.S. National Cancer Institute document: "Dictionary of Cancer Terms".: Hyperthermia therapy entry in the public domain NCI Dictionary of Cancer Terms
[3] Wolf, Peter (2008). Innovations in biological cancer therapy, a guide for patients and their relatives. Hannover: Naturasanitas. pp. 31–3. ISBN 978-3-9812416-1-7.
[4] Baronzio, Gian Franco; Hager, E. Dieter (2006). Hyperthermia in Cancer Treatment: A Primer. Medical Intelligence Unit. doi:10.1007/978-0-387-33441-7. ISBN 978-0-387-33440-0.[page needed]
[5] Mallory M, Gogineni E, Jones GC, Greer L, Simone CB 2nd (August 2015). "Therapeutic hyperthermia: The old, the new, and the upcoming". Crit Rev Oncol Hematol. 97 (15): 30018–4. doi:10.1016/j.critrevonc.2015.08.003. PMID 26315383.
[6] Y. L. Chang , N. A. Liu , L. Chen , X. L. Meng , Y. J. Liu , Y. P. Li and J. Y. Wang , J. Mater. Chem., 2012, 22 , 9594 —9601 RSC .
[7] D. Li , J. Tang , C. Wei , J. Guo , S. L. Wang , D. Chaudhary and C. C. Wang , Small, 2012, 8 , 2690 —2697 CrossRef CAS PubMed .
[8] Y. L. Chang , Y. P. Li , X. L. Meng , N. A. Liu , D. X. Sun , H. Liu and J. Y. Wang , Polym. Chem., 2013, 4 , 789 —794 RSC .
[9] Z. Luo , K. Y. Cai , Y. Hu , J. H. Li , X. W. Ding , B. L. Zhang , D. W. Xu , W. H. Yang and P. Liu , Adv. Mater., 2012, 24 , 431 —435 CrossRef CAS PubMed .