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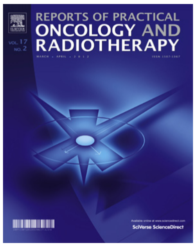

Review

Magnetic nanoparticle-based hyperthermia for cancer treatment

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ABSTRACT

Nanotechnology involves the study of nature at a very small scale, searching new properties and applications. The development of this area of knowledge affects greatly both biotechnology and medicine disciplines. The use of materials at the nanoscale, in particular magnetic nanoparticles, is currently a prominent topic in healthcare and life science. Due to their size-tunable physical and chemical properties, magnetic nanoparticles have demonstrated a wide range of applications ranging from medical diagnosis to treatment. Combining a high saturation magnetization with a properly functionalized surface, magnetic nanoparticles are provided with enhanced functionality that allows them to selectively attach to target cells or tissues and play their therapeutic role in them. In particular, iron oxide nanoparticles are being actively investigated to achieve highly efficient carcinogenic cell destruction through magnetic hyperthermia treatments. Hyperthermia in different approaches has been used combined with radiotherapy during the last decades, however, serious harmful secondary effects have been found in healthy tissues to be associated with these treatments. In this framework, nanotechnology provides a novel and original solution with magnetic hyperthermia, which is based on the use of magnetic nanoparticles to remotely induce local heat when a radiofrequency magnetic field is applied, provoking a temperature increase in those tissues and organs where the tumoral cells are present. Therefore, one important factor that determines the efficiency of this technique is the ability of magnetic nanoparticles to be driven and accumulated in the desired area inside the body. With this aim, magnetic nanoparticles must be strategically surface functionalized to selectively target the injured cells and tissues.

1. Background

Whereas Nanosciences involve the study and comprehension of nature at a very small scale, nanotechnology means the direct application of nanosciences to the development of new products, devices and techniques. Nanotechnology will become one of the leading fields of research and development in the present century, affecting practically all industries and economic sectors. It will involve disciplines like engineering,

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physics, chemistry, biology and medicine and its impact will be guaranteed in virtually all social and economic fields from healthcare to food, as well as in others, such as electronics, telecommunications, transportation, construction, textile or energy.

Specifically, healthcare and life science applications are becoming the most challenging and growing area for nanotechnology based systems and solutions. Nanostructured drugs and delivery systems targeted to specific sites in the body, biocompatible nanomaterials for replacement of damaged body parts, innovative bone and tissue reengineering technologies and reliable and cost effective lab-on-a-chip biosensors for cancer diagnosis are just a few examples of high value added by nanotechnology for applications in medicine.[1–3]

Nanoparticles are perhaps the most prominent nanomaterial in healthcare and life sciences. When particle size is reduced to the nanoscale (1–100 nm) materials exhibit remarkably unique size-dependent physical, chemical and biological properties. From the practical side of nanoparticles applied to medicine, the control and implementation of magnetic properties are among the most practical applications of nanoparticles for cancer diagnosis and treatment. Its research involves the design, synthesis and characterization of a wide variety of unconventional magnetic nanoparticles and core-shell nanostructures. Depending on particle size, composition, structure and physico-chemical properties, magnetic nanoparticles have demonstrated a diverse range of useful applications from magnetic resonance imaging, hyperthermia, separation or drug-delivery to catalysis.[4–6]

Radiation therapy or radiotherapy is based on the use of ionizing radiation to control or kill tumoral tissue. Tumor cells show an increased metabolism, higher rates of glycolysis and enhanced radiosensitivity as compared to normal cells, making them more vulnerable to radiation. The efficiency of radiotherapy relies on the irreversible damage that the ionizing radiation provokes to the DNA of injured cells, which eventually kills them or avoids their reproductive cycle, controlling in this way the progress of the tumor.

During the treatment of tumoral tissues with radiotherapy special care must be taken to avoid radiation exposure of surrounding healthy tissues in order to provide the patient with an improved quality life in the medium and long term future. In fact, one of the main aims of the new radiotherapy techniques has been to reduce the radiation dose affecting adjacent healthy organs or tissues while keeping the therapeutic dose to the tumoral ones.[7] In recent years, new techniques of treatment using radiotherapy (IGRT, VMAT, etc.)[8,9] have paid special attention on this issue, allowing a much better tumor control with reduced harmful side effects caused by high doses on healthy tissues adjacent to the treated tumor regions. It is important to remark that this reduction in the radiation dose affecting adjacent tissues or organs must never lead to underdose in the tumor areas, as this could eventually lead to local recurrence in the medium-term future.

As discussed above, radiotherapy treatment is performed at tissue or organ size scales, not at cellular level, so it is important to delimit as precisely as possible the volume of the injured region to be irradiated. This area delimitation also includes certain normal tissue that could be somehow affected by tumor cells and which is recommended to be removed in order to achieve a better control of the tumor. This issue is traditionally based on both clinical evidence and biochemical analysis of the tissue. Therefore, it is today a challenge to kill and control tumors at cellular level, for example using targets or markers able to identify and selectively attach to tumor cells, allowing a more localized treatment and eradication of the malign cells whereas the harmful secondary effects induced on the healthy ones would be significantly reduced.

Nowadays, the design of multifunctional nanoparticles are able to fulfill several requirements for a specific application is the basis of multidisciplinary approaches to the problem. In the case of biomedical applications, one of the main goals is to synthesize multifunctional magnetic nanoparticles that exhibit the highest saturation magnetization as possible and have surfaces properly functionalized that allow them to selectively attach to target cells or tissues.[10] DNA probes, antibodies and other chemical structures are commonly used to achieve this high demanded selectivity.[11] For a wide range of applications, the use of colloidal iron oxide and iron oxide-based core-shell nanostructures have attracted much attention.[12] Although other materials can be found that fulfill more appropriately the magnetic requirements for biomedical applications (i.e. materials with higher saturation magnetization), other concepts such as biocompatibility or toxicity must be taken into account. Iron oxides not only show interesting size-dependent magnetic properties and can be functionalized with both organic and inorganic compounds, but also they are thought to be biocompatible and non-toxic, which makes them excellent candidates for biomedical applications and in *in-vivo* experiments.[13]

2. MNP-based hyperthermia as anti-cancer therapy

Iron oxide based nanoparticles with superior magnetic properties and properly surface functionalized are being intensively investigated to achieve highly efficient carcinogenic cell destruction through hyperthermia treatments. In particular, it is difficult to find a definition for hyperthermia not linked to cancer therapy. Most definitions available of hyperthermia therapy come from health organizations or institutions. Here, we would like to cite one from the National Cancer Institute from United States of America, in which therapeutic hyperthermia is defined as: *A type of treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anticancer drugs*. This definition is not new. In fact, different approaches have been used to apply hyperthermia in tumor regions,[14] but with harmful secondary effects in the healthy tissues. This is the case of many techniques involving laser, ionizing radiation and microwaves[14] as tools to heat up malignant body tissues. Although these techniques are able to increase the intracellular temperature up to the cellular death, additionally they can provoke harmful side effects such as ionization of the genetic material or lack of selectiveness in radiation and microwaves therapies, respectively, that affect the surrounding healthy tissues. This encouraged the search of new mechanisms capable of increasing the temperature of damaged areas while keeping the rest of tissues healthy. Nanotechnology has just provided a novel and original solution to this problem with the magnetic hyperthermia. Magnetic hyperthermia allows to remotely induce local heat by means of the magnetic energy losses of magnetic nanoparticles under an oscillating magnetic field. In other words, the ability of some magnetic nanoparticles to transform the electromagnetic energy into heat allows the temperature increase in well- defined regions in the human body where the tumor cells and the nanoparticles are located. Therefore, the activation of these nanoparticles as nanoheaters can be controlled externally by applying or removing an oscillating magnetic field. The electromagnetic radiation used in magnetic hyperthermia is in the range of the radio-frequency (between several kHz and 1 MHz). This radiation is completely healthy and shows enough penetration depth to access inner organs or tissues in the body. The specificity of this technique is achieved by the higher sensitivity of the tumoral cells to temperature increases above 42°C, temperatures at which the natural enzymatic processes that keep the cells alive are destroyed, so that allowing their selective killing.[15] However, the apparent simplicity of the technique demands the fulfillment of several requirements to get the desired therapy effect. For biomedical applications, magnetic nanoparticles are preferred to show a superparamagnetic behavior,[16] meaning that the magnetization drops to zero when the applied magnetic field is removed. This fact implies that no coercive forces or remanence exist, preventing magnetic dipolar interactions between particles and, eventually, their aggregation, which could lead to serious adverse problems derived from the formation of clots in the blood circulation system. As previously indicated, the saturation magnetization should be also as high as possible in order to guarantee the efficient heating of the nanoparticles under the oscillating magnetic field. And this fact is very closely related to the particle size and distribution of the nanoparticles. The superparamagnetic properties of magnetic nanoparticles are size-dependent. An increase in the particle size will lead to higher saturation magnetization values and better performance for magnetic hyperthermia applications. However, this is true when the particle size is below a critical size above which magnetic nanoparticles become ferromagnetic (superparamagnetic limit), which is in principle an undesired magnetic behavior for biomedical applications due to a potential particle aggregation phenomena. On the other hand, the particle size is an issue of crucial interest in many biomedical applications in which the use of very small particles is highly desired to act as heat nano-sources in tumoral regions of limited size access. The commonest barrier found in most tissues is the continuous blood capillaries type, so the separation between the endothelial cells along the basement membrane will determine the efficiency of the hyperthermia therapy. A suitable balance should be found between the nanoparticles size distribution and their magnetic properties, because too small nanoparticles could not show hyperthermia effect whereas too big nanoparticles could not be able to cross the endothelial barrier through the continuous capillaries. In this way, the local heating would affect only the external tumor cells, while the inner ones would only experience a soft thermal effect, not enough to induce cell death.[17] Conversely, if the magnetic nanoparticles are small enough to cross the blood barrier, they could penetrate and distribute more homogeneously inside the tumor, provoking a heat diffusion that would kill a bigger number of neighboring tumor cells.

Other important requirement is related to the surface functionalization of the nanoparticles. All the nanoparticles used in biomedical applications are surface functionalized for several reasons: their physico-chemical properties should not be deteriorated in the medium (showing resistance against biological pH changes, hydrophobicity or hydrophilicity, etc.), they should be properly attached to ligands for specific recognition of the desired species (molecules, cells, tissues, organs) or to carry drugs that will be administered locally in the area of interest under certain internal or external stimuli.[11,18–20] Therefore, the success of using magnetic nanoparticles in biomedicine depends greatly on our ability to drive them to the target of interest.

There are several strategies of surface functionalization using different coating agents and biomolecules that help us to achieve this goal. Among them, we can mention polymers, viruses, antibodies (that specifically recognize proteins), aptamers (show high affinity to certain molecules), etc. In the particular case of magnetic nanoparticles, one of the most desirable administration routes is through intravenous injection, so the additional creation of sufficiently strong magnetic forces by means of permanent magnets could guide them to the target tissue, overcoming the blood flow forces naturally generated in the blood circulation system. Additionally to the preservation of the chemical–physical properties of the nanoparticles, a suitable particle surface modification or coating is also a useful tool to improve their biocompatibility and decrease as much as possible their toxicity, slipping past and avoiding the inmunosystem actuators. For hyperthermia therapy applications, it is very convenient that nanoparticles reach their target and stay in place long enough to allow a continued treatment, if necessary. Several multifunctional nanostructures are being widely researched for biomedical applications. Among them, we can emphasize core–shell nanostructures,[21] in which the shell not only can preserve the chemical and physical properties of the core, but also provide the nanoparticle with a more feasible surface to be further functionalized with organic and inorganic functional molecules and compounds. Dimers (two linked constituents) or labeled entities (i.e. virus with nanoparticles attached around it) are other complex structures usually investigated for biomedical applications. It is important to remark, that particle surface modification is an important parameter that should be taken carefully into account when researching the heating properties of magnetic nanoparticles for biomedical applications. Among other experimental parameters,[22] such as the frequency and amplitude of the electromagnetic oscillating field, size-dependent magnetic properties or solvent viscosity, the coating agent plays a key role for the specific absorption rate of nanoparticles for hyperthermia applications. Again, particle functionalization plays a crucial role in the hyperthermia performance, since an adequate nanoparticle surface modification improves largely their specificity and so, the higher the targeting specificity, the more selective killing of target cancer cells will be achieved. In hyperthermia related cancer therapy applications, the research is mainly focused on the design of more efficient nanoheaters. Also the hyperthermia response should be as high as possible, since high specific absorption rates imply lower time of residence of the nanoparticles in the human body and also lower dosages to be administered to the patient.

The killing of tumoral cells through the heat irradiated from the magnetic nanoparticles attached to them is a direct consequence of the heating properties of those magnetic nanoparticles under an applied alternating magnetic field. However, magnetic hyperthermia could allow other synergic actions in addition to the direct killing of the cancer cells. One example is the magnetically induced drug delivery. The design of intelligent drug delivery systems is a challenge in biomedicine due to its potential ability to provide an additional therapeutic treatment in the damaged area by controlled release of therapeutic agents. For example, one strategy to achieve this is to incorporate magnetic nanoparticles into thermoactive polymers or hydrogels, which can reversibly shrink and expand as a consequence of the temperature increase induced magnetically by hyperthermia effect, in such a way that they can deliver the loaded therapeutic drugs in a controlled way.[23]

To conclude, it just needs to be mentioned that the synthesis and characterization of these multifunctional nanoparticles involves the use of highly advanced electron microscopy techniques, such as high resolution transmission electron microscopy (HRTEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), as well as other cutting edge technologies, i.e. X-ray spectroscopy (XPS), X-ray diffraction (XRD) or vibrant sample magnetometers (VSM and SQUID-VSM). Comprehensive characterization guarantees nanoparticle size control, effectiveness of functionalization strategies and the achievement of the desired physico-chemical properties.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Bañobre-López M, Piñeiro-Redondo Y, De Santis R, et al. *J Appl Phys* 2011;**109**:07B313.
2. Tampieri A, D'Alessandro T, Sandri M, et al. *Acta Biomaterialia* 2012;**8**:843–51.
3. Gloria A, Russo T, D'Amora U, et al. *J R Soc Interface* 2013;**10**:20120833.
4. Pankhurst QA, Connolly J, Jones SK, Dobson J. *J Phys D: Appl Phys* 2003;**36**:R167–81.
5. Laurent S, Forge D, Port M, et al. *Chem Rev* 2008;**108**:2064.
6. Hadjipanayis CG, Bonder MJ, Balakrishnan S, Wang X, Mao H, Hadjipanayis GC. *Small* 2008;**4**(11):1925.
7. Piotrkowicz N, Zieliński J, Jońska J, Dębicki P. *Rep Pract Oncol Radiother* 2005;**10**(3):131.
8. Montero Perea E, Velazquez Miranda S, Rubio Jimenez M, Ortiz Seidel M. *Rep Pract Oncol Radiother* 2013;**18**(1):S352.
9. Gómez Aparicio M, Iglesias A, Martinez E, Escolar P, Salinas J. *Rep Pract Oncol Radiother* 2013;**18**(1):S264.
10. Yoo D, Lee J-H, Shin T-H, Cheon J. *Acc Chem Res* 2011;**44**(10):863–74.
11. Schladt TD, Schneider K, Schild H, Tremel W. *Dalton Trans* 2011;**40**:6315.
12. Cheong S, Ferguson P, Hermans IF, et al. *ChemPlusChem* 2012;**77**:135.
13. Campbell RB. *Nanomedicine* 2007;**2**:649.
14. Chicheł A, Skowronek J, Kubaszewska M, Kanikowski M. *Rep Pract Oncol Radiother* 2007;**12**(5):267.
15. Andra W, Nowak H. *Magnetism in Medicine: A Handbook*. first ed. Germany: Wiley-VCH; 1998.
16. Hofmann-Amtenbrink M, von Rechenberg B, Hofmann H. Superparamagnetic nanoparticles for biomedical applications. In: Tan MC, editor. *Nanostructured materials for biomedical applications*. 2009. p. 119. ISBN: 978-81-7895-397-7.
17. Rivas J, Bañobre-López M, Piñeiro-Redondo Y, Rivas B, López-Quintela MA. *J Magn Magn Mater* 2012;**324**:3499.
18. Frey NA, Peng S, Cheng K, Sun S. *Chem Soc Rev* 2009;**38**:2532.
19. Lattuada M, Alan Hatton T. *Langmuir* 2007;**23**:2158.
20. Lui A-H, Salabas EL, Schüth F. *Angew Chem Int Ed* 2007;**46**:1222.
21. Salgueiriño-Maceira V, Correa-Duarte M. *Adv Mater* 2007;**19**:4131.
22. Piñeiro-Redondo Y, Bañobre-López M, Pardiñas-Blanco I, Goya G, López-Quintela MA, Rivas J. *Nanoscale Res Lett* 2011;**6**:383.
23. Dionigi C, Piñeiro Y, Riminucci A, Bañobre M, Rivas J, Dediu V. *Appl Phys A* 2013, http://dx.doi.org/10.1007/s00339-013-7620-8 (in press).