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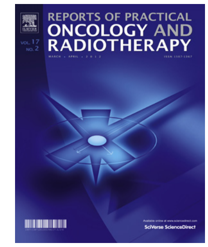

Review

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