The use of iron oxide nanoparticles in hyperthermia

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Introduction

Hyperthermia is a cancer treatment modality used as an adjunct to established therapies, like radiotherapy and chemotherapy. There are several techniques to induce hyperthermia, including the infusion of hot water for peritoneal and systemic hyperthermia, capacitive heating and inductive heating, radiofrequency and microwave radiation and ultrasound. Hyperthermia should be distinguished from thermal ablation. The latter works with a temperature rise greater than 50°C and by direct cell killing inside the tumor, whereas the former, also known as mild temperature hyperthermia or MTH, works in the temperature range of 39°C to 42°C by inducing more subtle effects.

Among the biophysical mechanisms, which render MTH effective, the most important ones are (1) the induction of a heat shock response and immune system stimulation, and (2) the increased blood flow in the tumor. The tumor core is frequently resistive to conventional treatments, like radiotherapy (since it is hypoxic) and chemotherapy (due to low drug supply). However, the increased blood perfusion induced by hyperthermia can enhance the damage of tumor cells at its center. Although hyperthermia has proven its efficacy with numerous phase III clinical trials [1-2], it has not gained the wide acceptance one would expect.

The major technical problem, which has delayed its promulgation, is the difficulty in heating the tumor region to the intended temperature while sparing the normal tissue. It appears that this problem can be solved by introducing the concept of intracellular hyperthermia; it is possible to deliver submicron magnetic particles inside the tumor cells and let them generate heat under an alternating magnetic field (AMF).

Nanoparticle properties

Among the nanoparticles that can be used for this purpose iron oxides, namely magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) are the most frequently used ones, due to their low toxicity and their known pathways of metabolism. However, there are other properties, such as biocompatibility, injectability and high absorption in the tumor cells, which the nanoparticles must possess in order to be used in hyperthermia. The size of nanoparticles determines to a large extend their suitability for the method in vivo.

There are two main issues that need to be tackled if the nanoparticles are to be injected in the main blood stream, i.e. glomerular filtration and opsonization. Kidneys will rapidly clear away from the blood particulate matter with a molecular weight less than about 40kDa (10mm) [3]. On the other hand, blood protein binding to the particles (opsonization) will make them a target of macrophage cells, which will remove them from the blood stream through phagocytosis and lead to their accumulation in organs like the liver, spleen, bone marrow and lymph nodes. Even when nanoparticles are wrapped within polymers, like dextran, starch or polyethylene glycol, a large percentage of them will eventually end up in these organs.

Delivery to the target

The most obvious way to avoid the above mentioned disadvantages of systemic nanoparticles administration is to inject them directly into the tumor. However, this is not always possible due to tumor location. Moreover, the dense extracellular matrices present in tumors do not allow in many cases the injection of enough nanoparticles to achieve the desired thermal result. It is, therefore, important to examine the delivery mechanisms of nanoparticles to the tumor target. If they stay in the blood stream long enough, there is a slow accumulation of them in the tumor for two reasons, namely extravasation, due to vascular leakiness, and faulty lymph drainage. The latter is responsible for the high interstitial pressure, which is another difficulty with direct injection. As a consequence, extravasated nanoparticles remain in the perivascular area and do not penetrate deeply into the tumor.

Another technique to deliver magnetic nanoparticles to the tumor site is termed ferromagnetic embolization hyperthermia [4]. Using this approach, the nanoparticles are injected to the feeding artery that supplies the tumor with blood. An excellent site of implementation for this technique is the liver, where tumors, contrary to the normal liver parenchyma, mainly derive their blood supply from the hepatic arterial system [5]. To facilitate cell adsorption of magnetic nanoparticles some researchers have proposed the use of magnetic cationic liposomes (MCL) [6]. The particles are wrapped in a phospholipid bilayer (liposome) with a positive surface charge, which

increases adsorption to tumor cells. Finally, the fabrication of antibody-conjugated nanoparticles is the best practice for the preferential accumulation inside the tumor [7].

Heat generation mechanism

If they are used in their pure form, i.e. not coated with a material to impede opsonization, the nanoparticles tend to agglomerate, building structures of a larger size, a fact which negatively influences their biomedical and magnetic properties. Ferromagnetic resonance (FMR) of iron's unpaired electron is a physical mechanism, which can produce heat. It takes place in the frequency range of 1MHz to 1000 MHz. Hysteretic heating can also occur in the frequency range of 50kHz to about 1MHz.

However, in the clinical practice and the experiments conducted so far, heating appears to be generated predominantly by the Néel and Brownian relaxations, since the sizes of the used nanoparticles is rather small (less than 30nm). Rosenweig [8] has proposed that the theoretical heat dissipation is proportional to the frequency and the squared strength of the externally applied AMF. Therefore, one would expect that high values of heat generation rates, expressed in terms of specific absorption rate (SAR), in the tissues could be achieved by increasing the magnetic field amplitude and frequency. However, this procedure is limited by the initiation of eddy currents in the patient's body. Eddy currents increase with the cross-sectional area of the body volume subjected to the AMF. This is perhaps why during the clinical application of the technique patients tolerated better the therapy in the head region, than in the pelvic and the upper thoracic regions, where they complained for discomfort (pain) [9]. Typical values of the AMF strength used at 100kHz are 8.5kA/m for tumors in the head (glioblastoma) and 3-5kA/m for pelvic tumors. The SAR for an 8kA/m field in a glioblastoma can reach a value larger than 700W/kg.

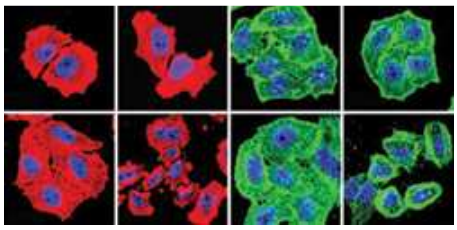

Fig.1. Cells exposed to nanoparticles (second row) and a magnetic field (second and fourth columns) display disrupted cytoskeletons [10]

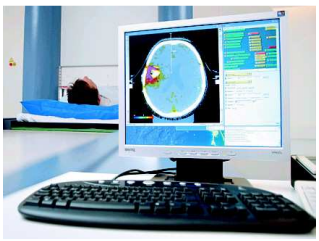

Fig.2. Iron-bearing nanoparticles injected directly into a brain tumor, heated using a focused magnetic field, weaken and even kill cancer cells [11]

Limitations of treatment

As mentioned above the main limitation of the treatment is the generation of eddy currents. Another exclusion criterion is the presence of metallic or active implants at a small distance from the treatment area (e.g. artificial hip joints for pelvic treatments, teeth's amalgam fillings or gold crowns for head and neck tumors, or cardiac pacemakers and implanted defibrillators).

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