Digest Journal of Nanomaterials and Biostructures Vol. 3, No.3, September 2008, p. 103 - 107

MAGNETIC NANOPARTICLES IMPACT ON TUMORAL CELLS IN THE TREATMENT BY MAGNETIC FLUID HYPERTHERMIA

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The heat-induced cell death with magnetic nanoparticles (MNPs) generates numerous cellular changes, leading to morphological changes, cell detachment, and death. Cellular alterations include, changes in the membrane, nuclear and cytoskeletal structures, cellular metabolism, macromolecular synthesis etc. In this work the purpose is to explain the main mechanisms of magnetic fluid hyperthermia (MFH), more precisely the heating mechanisms of MNPs and the effects of this heating on extracelullar and intracellular environments.

(Received May 3, 2008; accepted May 15, 2008)

Keywords: Magnetic nanoparticles (MNPs), Heating effect, Magnetic fluid, Cell death

1. Introduction

Magnetic fluid hyperthermia (MFH), i.e. the heating of tissue [1] using magnetic nanoparticles (MNPs), is a promising tool in the therapy of various cancers. This is because tumor cells are more sensitive to temperatures in the range of 42-45ºC than normal tissue cells [2]. There are several benefits to using hyperthermia. This process not only enhances the effectiveness of other cancer treatments, but it also kills tumor cells that are resistant to other forms of cancer treatment.

There are several methods of hyperthermia that are employed in cancer therapy: whole body hyperthermia, radiofrequency hyperthermia, inductive hyperthermia using a microwave antenna, implantable needles, and nanosized magnetic particles [3].

In this work, it is described the magnetic nanoparticles (MNP) heating theory [4-6] and the effects of MNPs on extra- and intracellular level [7].

It is crucial to understand the effect that the MFH process has on a cellular level. This paper will focus on the mechanisms of cellular destruction caused by MFH.

2. Theory and modelling of magnetic nanoparticles (MNPs)

There exist at least four different mechanisms by which magnetic materials can generate heat in an alternating field [8]:

1. generation of eddy currents in magnetic particles with size >1μ,
2. hysteresis losses in magnetic particles >1μ and multidomain magnetic particles,
3. relaxation losses in 'superparamagnetic' single-domain magnetic particles,
4. frictional losses in viscous suspensions.

Relaxation losses in single-domain MNPs fall into two modes: rotational (Brownian) mode and Néel mode. The principle of heat generation due to each individual mode is shown in

Fig. 1, (a) and (b). In the Néel mode, the magnetic moment originally locked along the crystal easy axis rotates away from that axis towards the external field. The Néel mechanism is analogous to the hysteresis loss in multi-domain magnetic particles whereby there is an 'internal friction' due to the movement of the magnetic moment in an external field that results in heat generation. In the Brownian mode, the whole particle oscillates towards the field with the moment locked along the crystal axis under the effect of a thermal force against a viscous drag in a suspending medium. This mechanism essentially represents the mechanical friction component in a given suspending medium.

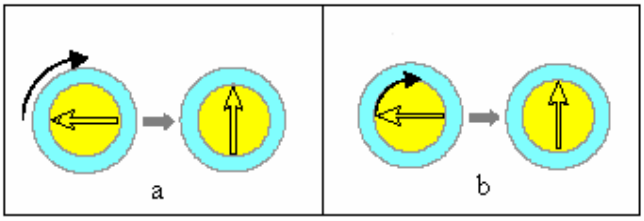

Fig. 1. Relaxation mechanisms of MNP: a - Brownian relaxation, entire particle rotates in fluid; b - Néel relaxation, direction of magnetization rotates in core. The structure of MNP: core (yellow), shell (blue). The arrow inside the core represents the direction of magnetization.

The energy dissipation of MNPs in an alternating magnetic is

$$P = \pi\mu_0\chi_0 H_0^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2} \tag{1}$$

where μ_0 is the permeability of free space, $4\pi\cdot 10^{-7}$ T m/A; χ_0 is the equilibrium susceptibility; H_0 and f are the amplitude and the frequency of alternating magnetic field; and τ is the effective relaxation time given by

$$\tau^{-1} = \tau_N^{-1} + \tau_B^{-1} \tag{2}$$

where τ_N and τ_B are the Néel relaxation and the Brownian relaxation time, respectively. τ_N and τ_B are written as

$$\tau_N = \frac{\sqrt{\pi}}{2}\tau_0 \frac{\exp(T)}{\sqrt{\Gamma}} \tag{3}$$

$$\tau_B = \frac{3\eta V_H}{kT} \tag{4}$$

where τ_0 is the average relaxation time in response to a thermal fluctuation; η is the viscosity of medium; V_H is the hydrodynamic volume of MNP; k is the Boltzmann constant, 1.38×10^{-23} J/K; T is the temperature. Here, $\Gamma = KV_M/kT$ and V_M is the volume of MNP. The MNP volume V_M and the hydrodynamic volume including the ligand layer V_H are written as

$$V_M = \frac{\pi D^3}{6} \tag{5}$$

$$V_H = \frac{\pi\left(D + 2\delta\right)^3}{6} \tag{6}$$

where D is the diameter of MNP; δ is the ligand layer thickness. The equilibrium susceptibility χ_0 is assumed to be the chord susceptibility corresponding to the Langevin equation, and expressed

$$\chi_0 = \chi_i \frac{3}{\xi}\left(\coth \xi - \frac{1}{\xi}\right) \tag{7}$$

where $\xi = \mu_0 M_d H V_M / kT$; $M_S = \phi M_d$; $H = H_0 \cos 2\pi f t$; and ϕ is the volume fraction of MNPs. Here, M_d and M_S are the domain and saturation magnetization, respectively. The initial susceptibility is given by

$$\chi_i = \mu_0 \phi M_d^2 V_M / 3kT \tag{8}$$

The temperature rise is calculated as $\Delta T = P\Delta t / \rho c_P$ where ρ and c_P are the effective density and the effective specific heat calculated as $\rho = \phi\rho_1 + (1-\phi)\rho_2$ and $c_P = \phi c_{P1} + (1-\phi)c_{P2}$, where subscripts 1 and 2 represent the MNPs and the medium, respectively.

3. Results and discutions

Majority of hyperthermic treatments not achieve uniform heating of the tumor region to the desired temperature without damaging normal tissue. Therefore, researchers have proposed intracellular hyperthermia by using nanosized magnetic particles [3]. MFH allows the heating to be restricted to the tumor area [9]. This method, which incorporates injecting the magnetic fluids directly into the tumor body, relies on the theory that any metallic objects when placed in an alternating magnetic field will have induced currents flowing within them [10]. As this occurs, the MNPs produce heat, as a product of resisting the current flow. With the application of an external AC magnetic field [11], the particles in turn heat the malignant cells when they come into contact, thus increasing the cells sensitivity to other treatments, ex. chemotherapy and radiation.

It was discovered that MNPs concentrated by an external constant magnetic field in tumor vasculature may lead to embolic lesions and necrosis of a tumor body and further the heat produced for thermal activation of a drug enhances the effect of chemotherapy by local hyperthermic treatment of neoplastic cells [12].

The results suggested that MNPs are potentially effective tools for the treatment of solid tumors, causing both killing of the tumor cells by heat, and the induction of an immune response [3].

Using magnetite particles, Ohno *et al.*'s strategy was based on the heat radiation associated with the physical process of hysteresis loss of magnetic substance in the alternative magnetic field [13]. Instead, though, they made a thin stick-type mingled with carboxymethylcellulose (CMC) to obtain a higher heating effect [13]. The benefit of this product was that one could much more easily direct the MNPs to their desired location. What was found

was that, by using CMC, the particles did not invade the surrounding normal tissue. In addition, the tumor sizes decreased, thus obtaining satisfactory results.

The response of the tumor to hyperthermia depends on the size of the tumor, its composition, physical location within the host tissue, and its vascularity [14]. During hyperthermia, the tumor bed does not vasodilate – therefore, blood flow can't increase and heat is retained in the tumor tissue at temperatures that would have caused normal capillary beds to vasodilate [14]. The growth of solid tumors is associated with the incorporation of fluid within the tumor mass as a result of nutrient deprivation, which can constitute up to 60 percent of the tumor volume [14]. This fluid, however, is void of oxygen and glucose, and contains excessive amounts of carbon dioxide and lactic acid. Under conditions of extreme nutrient deprivation, cell death occurs rapidly at 37ºC and even quicker at higher temperatures [14]. An increase in the temperature of this fluid may lead to an increase in the hydrostatic pressure due to the increase in molecular motion [14].

Cell death occurs in two modes, *apoptosis* and *necrosis*, that are biochemically and morphologically different [15].

Apoptosis: Apoptosis is a genetically programmed and biochemically active mode of death in which the cell actively participates in its own elimination [15]. It is required for cell life span and normal development [16]. Apoptosis aids in self-deletion of injured cells, terminal differentiation of epithelial cells, and organ and tissue shaping [15]. Abnormalities of this process are implicated in several human diseases, including cancer.

This process can be recognized by cell shrinking, condensation of the chromatin, and eventually DNA fragmentation [15]. In addition, actin is considered to play a role in several main morphological events of apoptosis, including formation of blebs, cell rounding, detachment, and final cell disintegration into apoptotic bodies [16].

Cells inducing apoptosis retain much of their membrane function and do not elicit an inflammatory response [15]. This process can be triggered by radiation, transduced signals, DNA damage, and hyperthermia. Furthermore, hyperthermia with a temperature range of 41-45ºC induces apoptosis to varying degrees in many cell lines [15]. The mechanism behind hyperthermia-induced apoptosis, however, isn't well understood. Some postulate that the primary targets are heat liable and newly synthesized proteins. These denatured proteins and unfolded nascent peptides can be cytotoxic and lead to cell death [15]. In addition, heat shock proteins act by preventing the aggregation of the denatured proteins through interactions with the ATP pathway [15]. Targeted proteins must go through the ATP pathway before they can be recognized as substrates for proteolysis. Therefore, when hyperthermia is induced on the cells, the proteins denature before the heat shock protein response can occur. It is logical to assume, then, that by administering hyperthermia, the cell can accumulate high does of heat shock proteins [15]. Some hypothesize that by inhibiting the synthesis of the heat shock proteins, the cells is unable to build a pool of protective stress proteins, and the cell loses its capability to survive [15].

Necrosis: Cells subject to toxic insult die by necrosis [17]. In this case, metabolic functions stop, which therefore causes a lack of osmotic regulation, thereby inflicting cellular swelling [17]. In addition, necrosis causes a sharp decline in ATP production, mitochondrial swelling, and eventually cytolysis and the release of pro-inflammatory agents [15]. Unlike apoptosis, these reactions occur as a natural result of loss of cell function. Although it has been widely accepted that hyperthermia always caused necrosis, it is now clear that this isn't the case [18]. Rather, hyperthermia induces apoptosis in neoplastic cells and tissues.

4. Conclusions

This paper reviews the theoretical background of MNPs used in magnetic fluid hyperthermia and some of the cellular affects resulting from MFH. To summarize, tumor cells are more susceptible to high temperatures, thus allowing MFH to actually kill the malignant cells. Apoptosis, not necrosis, is one result of hyperthermia. High heat subjected to cells drastically affects the cellular components and pH is an important factor of the tumor cell death. And lastly, MNPs are emerging as a potential substance to increase the effectiveness of hyperthermia.

The future possibilities of this anti-cancer precursor are nearly endless. For example, researchers could soon use MFH treatments to completely inactivate the manifestation of HIV, thus allowing the patients to live a longer life. Further, MFH treatments may soon cure cancers such as leukemia. Although MFH is a relatively new treatment used for cancer, it has already changed the lives of many people.

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