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Magnetic properties and antitumor effect of nanocomplexes of iron oxide and doxorubicin

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Abstract

We present a technology and magneto-mechanical milling chamber for the magneto-mechano-chemical synthesis (MMCS) of magneto-sensitive complex nanoparticles (MNC) comprising nanoparticles Fe_3O_4 and anticancer drug doxorubicin (DOXO). Magnetic properties of MNC were studied with vibrating magnetometer and electron paramagnetic resonance. Under the influence of mechano-chemical and MMCS, the complex show a hysteresis curve, which is typical for soft ferromagnetic materials. We also demonstrate that Lewis lung carcinoma had a hysteresis loop typical for a weak soft ferromagnet in contrast to surrounding tissues, which were diamagnetic. Combined action of constant magnetic field and radio frequency moderate inductive hyperthermia (RFH) below 40 °C and MNC was found to induce greater antitumor and antimetastatic effects as compared to conventional DOXO. Radiospectroscopy shows minimal activity of FeS-protein electron transport chain of mitochondria, and an increase in the content of non-heme iron complexes with nitric oxide in the tumor tissues under the influence of RFH and MNC.

From the Clinical Editor: This study reports on the top-down synthesis of magneto-sensitive complex nanoparticles comprised of Fe_3O_4 nanoparticles and doxorubicin. Authors also found that Lewis lung carcinoma had a hysteresis loop typical for a weak soft ferromagnet in contrast to surrounding tissues, which were diamagnetic. Combined action of constant magnetic field and radio frequency induced moderate hyperthermia induced both antitumor and antimetastatic effects greater than conventional DOX alone.
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Key words: Magneto-mechano-chemical synthesis; Magnetic nanoparticles; Free radicals; Doxorubicin; Lewis lung carcinoma

Magnetic nanotherapeutics is based on the utilization a combination of magnetic nanoparticles, either on their own or conjugated with other moieties such as anticancer drugs, and, external magnetic fields that serve to either guide the nanoparticles toward the tumor and/or excite the nanoparticles. Magnetic nanoparticle hyperthermia, for example, is a well-known thermotherapy that has been recently shown to be effective in the treatment of brain tumors.[1] Magnetic nanoparticles injected into tumors have been heated, depending on the particle size distribution and frequency range used, by a combination of hysteric loss, Neel and Browninan type relaxation under the influence of an external alternating magnetic field. By raising the temperatures of tumor tissues above 42 °C, apoptosis can be induced, while temperatures higher 45 °C can directly kill cells.[2] Magnetic nanoparticle hyperthermia appears well-suited as an

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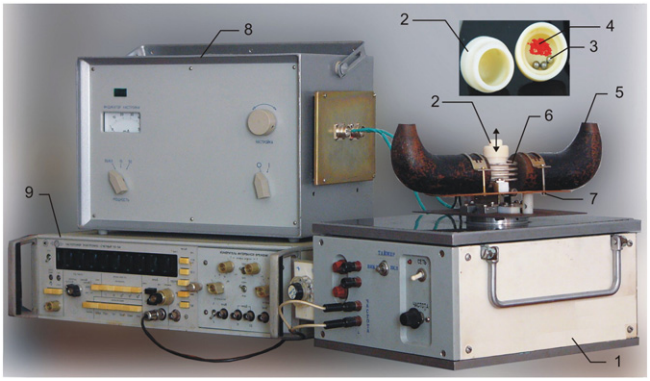

Figure 1. Magneto-mechanical milling chamber: 1 – mechanical chamber; 2 – diamagnetic chamber; 3 – metallic balls; 4 – Fe_3O_4, KCl and DOXO; 5 – permanent magnets; 6 – inductor; 7 – inductor stand and permanent magnets; 8 – master generator; 9 – frequency meter.

effective tumor therapy: (1) the concentration of nanoparticles in the tumor is both sufficiently high and significantly higher than in surrounding, normal tissue, (2) the use of nanoparticles, which can combine both therapeutic and diagnostic capabilities in one dose, has the potential to lead toward personalized oncology and better outcomes for patients, (3) the particles possess a high enough specific absorption rate. However, there are a number of limitations of magnetic nanoparticle hyperthermia such as: (1) therapy by nanoparticles in the temperature range 43-70 °C can be accompanied by the formation of drug resistance due to the induction of heat shock proteins, (2) the temperature above 45 °C may shut down tumor tissue perfusion, and (3) targeted therapy with magnetic nanoparticles is often not suitable for disseminated and abdominal tumors.[3,4]

In this paper we propose a fundamentally different approach from the magnetic nanoparticle hyperthermia. The proposed technology is based on the utilization of nanoparticles loaded with anticancer drugs and guided toward the tumor site to selectively destroy it in conjunction with electromagnetic excitation.

Cancer development can be thought as a multi-stage process involving initiation, promotion and progression, each one of these involving the action of reactive oxygen species and other free radicals. It is well known that the cumulative increase and unbalance of reactive oxygen species (ROS) known as oxidative stress, play a role in the carcinogenesis and subsequent tumor growth. Low and moderate levels of oxidative stress facilitate the initiation and promotion of the cancerous cell, whereas, high levels of oxidative stress can lead to apoptosis or necrosis.[5] Cancer cells are then particularly vulnerable to an oxidative assault[6] and induction of high levels of oxidative stress in tumor tissue that has the potential to destroy or arrest the growth of cancer cells can be thought of as therapeutic strategy against cancer.[7] Furthermore, one of the known mechanisms of antitumor activity of anthracyclines, like DOXO, is the generation of free radicals. DOXO undergoes a redox-cycling reaction during which superoxide and hydrogen peroxide (ROS) are produced. Subsequently, iron ions can catalyze the generation of hydrogen radicals from hydrogen peroxide by Fenton-type reaction, the formation of which can break mitochondria, lipids, proteins, DNA and other structures in tumor cells and finally lead to apoptosis or necrosis. Cancer cells sequester iron to aid in proliferation so overdosing cells with iron may be a mechanism to inhibit cancer progression.

We propose to use iron-oxide nanoparticles conjugated with doxorubicin to generate an oxidative assault for cancer therapy. Iron oxide nanoparticles are the most commonly used nanoparticles due to their biodegradable nature, biocompatibility, superparamagnetic effects. Magnetite Fe_3O_4 is a material with a high saturation magnetic moment m_s in a wide range of temperatures. Some of the known methods for synthesis of the complex of iron oxide nanoparticles are oxidization, chemisorption on their surface, directed modification of surface, thermolysis, mechano-chemical activation.[8] The mechano-chemical activation of antitumor drug doxorubicin (DOXO) results in increased concentration of free radicals that may increase the degree of polarization of spin states.[9] We have previously reported on a technique, which we call magneto-mechano-chemical synthesis, for the fabrication of magneto-sensitive complex nanoparticles (herein abbreviated as MNC).[10] The method is based on the integration of two known methods: mechano-chemical synthesis[11] and synthesis of enzymes in a milling-chamber with magnetic elements.[12] The principle of the mechano-chemical synthesis is based on the fragmentation and formation of an ensemble of paramagnetic centers, such as free radicals in the complex nanoparticle structure.[13] For singlet geminate radical pairs, the low field effect leads to a boost in the concentration of free radicals, which may be relevant in the context of in vivo biological effects of electromagnetic fields.[14] Iron oxide nanoparticles could participate in electron transfer reactions that lead to the production of free radicals. The increase in the concentration of free radicals of the MNC is suggestive of the potential increase of the drug antitumor effect under the influence of external radio frequency energy.[15] Furthermore, magnetic field gradients near physically realistic nanostructures were theoretically predicted to induce of heterogeneous reactions involving free radicals in processes of catalytic oxidation into tumor.[16] The effect of magnetic interactions on the rate of enzymatic synthesis of ATP in vitro that is of relevance to redox reactions was recently reported.[17]

In addition we propose to use in conjunction with the injection of the nanoparticles an external electromagnetic irradiation (EI) to further disrupt the free radical metabolism, increase the free radical lifetime and increase their concentration locally.

Interestingly, it is known that some but not all malignant tumors show weak ferromagnetic properties because they can store ferromagnetic ferric oxide.[18] In this paper, Lewis lung carcinoma, which originates spontaneously as a carcinoma of the lung in C57BL mice, is shown to exhibit ferromagnetism and can thus be used in model studies. Most of the ferromagnetic crystals in Lewis lung tumor show coercivities ranging from 20 to 30 mT. In comparison, control samples of muscle and connective tissue from healthy C57BL/6 mice display only very weak coercivities of 32 pT. We expect, that such a tumor may be susceptible to the therapeutic approach suggested here and therefore we selected to study the effect of the magnetic nanocomplexes and EI on Lewis lung carcinoma.

In this study, we have carried out a comparative analysis of magnetic properties of nanocomplexes comprising magnetic nanoparticles and DOXO synthesized by the new method of magneto-mechano-chemical synthesis and their antitumor effects in the treatment of Lewis lung carcinoma, in vivo.

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