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Oh the Irony: Iron as a Cancer Cause or Cure?

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Abstract

Iron-oxide nanoparticles facilitate cancer diagnosis through enhanced contrast, selectively enhance tumor cell death with magnetic hyperthermia, and improve drug delivery with magnetic drug targeting. One application that remains largely unexplored is using the iron-oxide nanoparticles themselves to selectively inhibit tumor growth. In this leading opinion paper, we propose that high doses of iron-oxide nanoparticles can be used as a treatment for cancer by generating an oxidative assault against cancer. This proposal may be met with resistance considering the controversy surrounding iron in the field of cancer. Iron generates reactive oxygen species through the Fenton reaction, which may both cause – or cure cancer. Additionally, high demand for iron by cancer cells leads to contradictory therapeutic approaches: iron deprivation or overdose are both potential cancer therapies.

Introduction

There are two controversies surrounding iron in the field of cancer. The first is that iron, in its elemental state, can generate reactive oxygen species (ROS) that may cause or prevent cancer. The second is that manipulating tumor iron stores can inhibit cancer growth *via* iron depletion or iron overload. One application of magnetic nanoparticles largely unexplored in cancer therapy is their potential to inhibit tumor growth through iron overload. We propose that high doses of iron-oxide nanoparticles on their own may be used to generate an oxidative assault for cancer therapy. A schematic connecting the role of iron in cancer and nanoparticle applications is shown in Figure 1.

A Cause and a Cure: Iron Generated Oxidative Stress

Chronic oxidative stress is one of the mechanisms by which malignant transformation occurs; however, selective induction of acutely high levels of oxidative stress in tumor tissue has the potential to destroy and/or arrest the growth of cancer cells [1]. Iron is toxic in its elemental state; free ferrous iron (Fe^{2+}) can participate in the Fenton reaction¹, producing the highly toxic hydroxyl radical ($\bullet\text{OH}$). Increased iron consumption or high body iron stores may lead to increased incidence of a variety of cancers in humans through increased oxidative stress [2–5]. Thus, because of its known ability to generate DNA damaging

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hydroxyl radicals and potentially cause cancer, the potential to have free iron in the body is generally a cause for concern.

On the other hand, cancer cells are generally deficient in the antioxidant enzymes present in normal cells [6], making them particularly vulnerable to an oxidative assault. The metabolic demands of cancer cells manifest in increased levels of transferrin receptors to facilitate iron uptake, and decreased levels of ferroportin (an iron export protein) to control iron homeostasis compared to normal cells [7]. The differences in iron metabolism between cancer cells and normal cells suggest an iron-mediated oxidative assault may be a mechanism for selectively targeting cancer cells while leaving normal cells unharmed [6].

Manipulating Tumor Iron Stores for Cancer Therapy

Disrupting tumor iron stores through iron depletion or iron overload results in growth arrest. One potential therapeutic approach in cancer cell manipulation is to rob cancer cells of this essential nutrient with iron chelators. Desferal (desferrioxamine mesylate) is clinically approved for the treatment of iron overload as an anti-cancer therapeutic in animal models and clinical trials [8, 9]. Iron chelators cause growth arrest in some tumors, though their real utility may be in the use as a combination therapy with Doxorubicin to prevent the iron mediated cardiotoxicity associated with administration of Doxorubicin [8, 9]. Because of the limited success of iron chelation in cancer therapy and a need for more potent chelators to be developed, we propose that manipulating iron stores in the other direction, i.e. causing iron overload, will be a more successful therapeutic approach for the treatment of cancer.

The idea that iron-overload can selectively inhibit tumor growth holds true in practice: in an aggressive T-cell lymphoma, blocked production of the iron storage protein ferritin heavy chain led to an increase in the free intracellular iron stores, ROS, and resulted in decreased tumor growth while normal cells were unharmed [10]. The antianemic iron therapy Ferric-Sorbitol-Citrate ablates a variety of cancerous cells but not normal cells *in vitro*, and inhibits murine melanoma B16 cells *in vivo* [11]. The idea then, that iron overload can be used to selectively inhibit cancer growth while leaving normal cells unharmed has been recognized, but the best way to achieve this result remains largely unexplored.

Multifunctional Magnetic Nanoparticles: A Potential Cancer Therapy

There is widespread use of magnetic nanoparticles as tumor contrast agents, and many applications for combined diagnostic and therapeutic platforms (including targeted drug delivery and hyperthermia) exist [12–14]. However, there are a limited number of studies that examine the long-term effect of iron-oxide nanoparticle formulations on tumor growth and animal survival that include plain nanoparticle controls.

Nanoparticles that were designed for magnetic hyperthermia show a slight decrease in tumor growth after treatment with plain particles without exposure to the alternating magnetic field treatment; in this instance the authors speculate that it is oxidative stress generated as the iron-oxide is broken down [15, 16]. A separate study that examined the effects of targeted iron-oxide nanoparticle delivery to the brain *via* convection enhanced delivery found a significant increase in survival of the non-targeted particles (16 days) compared to the HBSS

¹Fenton Reaction:

control (11 days) [17]. In this case, the targeted iron-oxide nanoparticles increased the survival in the glioblastoma model to 19 days [17].

In our own laboratory, we have found that a single dose of iron-oxide nanoparticles containing 1.1 mg of iron effectively decreases tumor size and increases survival in athymic nude mice bearing MCF-7 xenograft tumors (data not published). Assuming that the average human is 70 kg and has 3 g of total iron body stores, we estimate that a 25 g mouse in our study would have 1.1 mg of iron. Thus, in a single injection we treat the mice with a dose of iron roughly equivalent to that of their total iron body stores. In considering whether this would be clinically feasible, there are some clinical situations where patients require iron replacement therapy of up to 3.6 g [18]. The current clinical formulations limit the amount of IV iron administered to a max of 20 mg/kg in a single rapid infusion, or 1400 mg in a 70 kg person, delivered weekly until the total required iron dose is met. The limitations of the amount of iron that can be given in a single dose is due in part to the hypersensitivities associated with the formulations [19]. Our iron-oxide formulation, which does not use dextran, may offer a safer alternative and increase the dose that can be delivered intravenously. Lower, repeated doses may also effectively inhibit cancer growth but this remains to be tested.

Not all long-term *in vivo* studies support this theory that iron-oxide nanoparticles on their own can be used for tumor ablation. Iron-oxide particles targeted to the Her-2 receptor over-expressed on the mouse fibroblast cells NIH3T6.7 had growth patterns similar to the control [20]. This may be in part due to the cell type, as other studies involving the mouse fibroblast cell line L929 show iron does not generate a toxic effect [11].

One additional noteworthy observation with our magnetic nanoparticle formulation is that it is non-toxic *in vitro*, but there is selective toxicity to cancer cells *in vivo* and a decrease in tumor growth compared to the control saline. This contrasts the results observed with the antianemic iron therapy iron-sorbitol-citrate, which ablates a variety of cancerous cells but not normal cells *in vitro*, and inhibits murine melanoma B16 cells *in vivo* [11, 21]. The differences in the formulation of the iron may be why these particles have been identified to ablate cancer cells *in vitro* while iron-oxide nanoparticles are typically considered to be non-toxic *in vitro*. Iron-oxide nanoparticles must first be broken down before entering into the Fenton reaction, which may not happen in cell culture. On the other hand, the iron replacement therapies contain ferric iron, which may more readily interact to inhibit cell growth or be more easily converted to ferrous iron *in vitro* and enter into the Fenton reaction.

Controversies Surrounding Iron Therapy

Iron plays a central role in many biological processes, and is tightly regulated by the body. There are many clinical situations where iron stores are depleted and must be replaced including non-dialysis dependent chronic kidney disease, inflammatory bowel disease, obstetrics, menorrhagia, and anemia as a result of cancer therapy [22]. The challenges associated with iron replacement therapy surround the toxicity of iron in its elemental state, the required dose and rate of repletion, and hypersensitivities and toxicities associated injectable formulations. Iron has been formulated in a variety of different complexes for the clinical applications including iron isomaltoside 1000 (Monofer), iron-sorbitol-citrate (Jectofer, no longer manufactured), sodium ferric gluconate (Ferrlecit), iron sucrose (Venofer), and low molecular weight iron dextran (CosmoFer, InFed) or high-molecular-weight iron dextran (DexFerrum). Adverse drug events and hypersensitivities are associated with many of the formulations, but the real controversy surrounds low- and high-molecular weight iron dextran. High-molecular-weight iron dextran is associated with a greater number

of adverse events, and is often considered a less-expensive alternative to low-molecular-weight iron dextran, resulting in administration of the high-molecular weight formulation when the low-molecular weight formulation is often ordered [19, 23]. Fear of the adverse drug events may lead to inappropriate underuse of the iron-replacement therapies that may not be resolved until high-molecular-weight iron dextran formulations are abandoned in clinical practice [23].

The controversies surrounding iron and its ability to generate oxidative stress and potentially cancer lead to conflicting recommendations regarding iron therapy for anemic cancer patients [22, 24]. The carcinogenicity of the iron-dextran therapy was fairly well studied beginning in the 1960's, after a 1959 report that weekly high doses of intramuscular injections of iron-dextran formed sarcomas in rats [25]. The authors commented that for the iron to be tumorigenic in rats, the work required 200–300 times the amount that is generally recommended in humans [25]. These results do not hold true in all animal models, and for all the fear associated with iron as protumorigenic, there are relatively few reported cases of iron therapy causing new tumors in humans [26]. A study of a man with chronic blood loss was treated with nearly 69 g of iron supplement over the course of 10 years, and had no signs of sarcomas [27]. There are a few studies that have reported the formation of tumors in patients after iron replacement therapy, though not all cases were attributed to the iron injection, and considering the number of patients given of iron replacement therapy, the risk of tumor formation as a result of iron therapy, while it does exist, is relatively low [26].

Harnessing the oxidative potential of iron as a therapy may be an additional way to maximize its potential in cancer treatment, in addition to the many diseases, including cancer, that require iron supplement therapy. There are limitations, however, to traditional iron replacement therapies that may make iron-oxide nanoparticles a more advantageous choice for therapies against cancer. The iron-therapies, from their widespread use in chronic kidney disease, are known to have hypersensitivities associated with the high molecular weight dextran-complexes in particular. The adverse drug events often limit the amount of iron that can be delivered in a single dose, and may require a test dose.

Other Biomedical Applications of Iron

In addition to its application for cancer therapy, iron-based nanoparticles due to their inherent magnetic property have been explored for other biomedical applications. The high magnetization of iron-oxide nanoparticles allows them to be used as an effective negative contrast agent for cancer, heart diseases, etc. In the fields of tissue engineering and regenerative medicine, iron-oxide particles offer a means to both guide and track the location of transplanted cells *in vivo* [28, 29]. Cells labeled with magnetic particles increase intracellular gene delivery and aid in the formation of cell sheets to promote vascularization [30]. Labeling of cells with magnetic nanoparticles has an additional multifunctional advantage because the anatomic location of the cells can be tracked longitudinally *via* magnetic resonance imaging [31].

Iron-oxide based nanoparticles can be used in a variety of purposes in cancer related diagnostics and therapy. Magnetic beads are used clinically to separate and detect circulating tumor cells from whole blood and can be used to estimate the overall and progression free survival of patients with metastatic breast cancer earlier than traditional imaging methods [32, 33]. The magnetic properties allow magnetic particles containing drug to be directed to superficial tumors with an externally applied magnetic field, increasing the local drug concentration [14, 34]. On their own, magnetic nanoparticles can generate local hyperthermia with application of an externally applied magnetic field, selectively ablating tumor cells through local generation of high temperatures [15, 35]. In combination, magnetic

nanoparticle induced hyperthermia further enhances the effectiveness of therapeutic agents such as cisplatin possibly due to membrane permeabilization [36].

Leading Opinion

The altered regulation of iron in cancerous cells compared to normal cells, along with the potential for iron mis-regulation to selectively cause oxidative stress and cell death makes iron overload an attractive therapeutic idea for the treatment of cancers. We propose that high doses of iron-oxide nanoparticles may be used to generate an oxidative assault for cancer therapy. Compared to iron replacement formulations as a therapeutic agent, the magnetic nanoparticles will offer multifunctional applications for the diagnosis, combined therapeutic potential, and monitoring of progression of the disease. Further, the iron in magnetic nanoparticles is not stored in its elemental form, which may reduce some of the associated toxicity. There may be dose dependent effects of iron required for tumor ablation. Whether ablation is achieved through a single high dose, or can be achieved with multiple smaller doses remains to be elucidated. Higher doses may be better achieved through development of new formulations, which could have fewer adverse drug events than current iron therapies.

As a supplement to current treatments where iron-oxide nanoparticles will be used in diagnosis or therapy with magnetic hyperthermia and drug delivery, iron-based formulations may boost the local oxidative stress and enhance the tumor cell death. With the development of many multifunctional formulations, challenges include achieving optimal tumor kill from each aspect of the formulation, without compromising the activity of the other applications. For combined iron-drug therapy, the drug administered, or even the order - before, with, or after - magnetic nanoparticle injection may drastically alter the activity as was observed with combined cisplatin/hyperthermia therapy. While magnetic nanoparticles localize to the tumors passively through the enhanced permeability and retention effect, a targeted formulation may further increase the effectiveness of the proposed therapy. Local delivery of the iron-oxide through targeting by a magnetic field or through receptors over-expressed on the cell surface should be explored.

Because of the potential for iron to generate cancer, and the past history of sarcoma formation in rats and in a few cases in humans, the idea of using iron based particles as a tumor therapy in humans will likely be met with resistance. However, the cellular nature of cancer, its increased need for iron, ability to sequester iron, inability to expel iron, and general elevated levels of oxidative stress could make iron an ideal therapy. The past work on iron replacement therapies and current work on multifunctional magnetic nanoparticles have laid a strong foundation for exploring iron as a potential therapeutic and we look forward to future developments in this field.

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Figure 1. Role of Iron in cancer progression and treatment

Iron can generate reactive oxygen species (ROS) through the Fenton reaction, leading to DNA damage and carcinogenesis in healthy cells, or contribute to cell death in tumors. Cancer cells sequester iron to aid in proliferation; removing this essential nutrient with iron chelators or overdosing cells with iron to cause oxidative damage are two mechanisms to inhibit cancer progression. Iron based nanoparticles may increase intratumoral iron and generate an oxidative assault leading to tumor regression. Nanoparticles have further multifunctional applications in cancer diagnosis (magnetic resonance imaging and detection of circulating tumor cells) and therapy through magnetic hyperthermia and magnetic drug targeting.