Lanthanum fluoride particles to enhance radiation therapy

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Lanthanum fluoride particles passively collect in tumors and amplify applied radiation doses, while also transferring energy to photosensitizer dyes that enable the targeting of cancerous cells.

Nanoparticles have been called a ‘new paradigm’ for cancer diagnosis and treatment. The leaky blood vessels found in tumors (and other inflamed tissue) permit the accumulation of nanomaterials smaller than 400nm at much greater levels than is seen in healthy tissue. This is called the ‘enhanced permeability and retention’ (EPR) effect, and it enables passive targeting of cancer using nanoparticles of organic materials. Examples of these include polymers, metal particles such as gold, and semiconductor particles such as quantum dots. The materials may be conjugated to antibodies or peptides directed to targets expressed on cancer cells to further improve targeting. The effect is already in use in the clinic for delivery of anti-cancer drugs encapsulated in liposomes, such as the highly effective liposomal doxorubicin. However, solid nanoparticles have not yet been tested in human cancers. The goal of our work is to develop a solid nanoparticle that will accumulate in tumors and result in greater effectiveness of radiation therapy.

Over half of cancer patients receive radiation therapy, which can be kilo- or mega-voltage x-rays, gamma-rays, or other types of radiation. High atomic number (high-Z) materials can increase the effective dose of radiation in areas where they concentrate. Combined with the EPR effect, this can lead to radiosensitization of tumor tissue, potentially leading to protocols for radiation therapy that are increasingly effective against cancer and less harmful to surrounding normal tissue.

High-Z contrast media, such as iodine and gadolinium, have traditionally been used to increase the effective radiation dose. In recent years, biologically compatible nanoparticles have been successfully demonstrated in theoretical models, cell systems, and animals. The most commonly used material is gold. Gold nanoparticles show no evidence of toxicity to target organs, and are rapidly eliminated through the kidney. Theoretical studies are used to quantify the dose enhancement, which depends upon gold concentration and beam quality.

The result of these studies has been the birth of a radiation treatment modality referred to as gold nanoparticle-aided radiation therapy (GNRT). GNRT has been shown to be effective in mouse models of breast cancer, prostate cancer, and melanoma. However, the amount of gold needed for each patient greatly increases the cost of the treatment. In addition, the dose enhancement seen with untargeted gold particles under typical radiation therapy protocols is at best a few percent. For this reason, researchers have sought alternative high-Z materials for nanoparticle-aided radiation therapy. One of the most promising in both theoretical and cell studies is lanthanum fluoride (LaF$_3$).

The primary hypothesis behind our work is that LaF$_3$ nanoparticles doped with cerium and terbium (LaF$_3$:Ce,Tb) will be more effective in killing cultured cancer cells than gold nanoparticles under kilo-voltage x-ray therapy. The effect would be enhanced still further if the particles were conjugated to a dye that absorbs in the range of the nanoparticle emission. Our goal was to synthesize and characterize LaF$_3$:Ce,Tb nanoparticles, conjugate them to a targeting peptide and/or a...
photosensitizer dye, and test them against cultured cancer cells under x-ray application.

We achieved successful synthesis and biofunctionalization of LaF$_3$:Ce,Tb nanoparticles, with a novel surface coating that makes them stable in cell culture media. We showed that the particles emit under x-ray excitation using therapeutic energies and dose rates. The spectra seen under x-ray excitation are similar to those seen using light excitation, something that had not previously been tested: see Figure 1(A). We then established energy transfer between the particles to the photosensitizer dyes by steady-state and time-resolved emission spectroscopy: see Figure 1(B). Finally, we established protocols for testing anti-cancer cell efficacy using colony-forming assays. These assays measure the ability of cells to divide after treatment, and are essential for measuring the efficacy of radiation treatments, since radiation prevents cell division but does not kill the cells outright.

In summary, we have produced a formulation of LaF$_3$:Ce,Tb conjugates that is non-toxic to cells, making this construct ready for anti-cancer testing in cell lines. Our future work involves extensive testing of the efficacy of bare and conjugated LaF$_3$ nanoparticles against a variety of cancer cell lines in vitro. We will load nanoparticles into cells and expose them to therapeutic doses of x-rays, and we will use colony-forming assays to quantify inhibition of cell reproduction resulting from the radiation.

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**References**