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Commentary

Suicide Gene Delivery by Calcium Phosphate Nanoparticles

A Novel Method of Targeted Therapy for Gastric Cancer

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suicide gene therapy, gastric cancer, calcium phosphate, nanoparticles, cytosine deaminase, carcinoembryonic antigen

ABBREVIATIONS

5-FU	5-fluorouracil
bCD	bacterial cytosine deaminase
GCV	ganciclovir
YCD	yeast cytosine deaminase
HSV-1 TK	herpes simplex type 1 thymidine kinase
CPNP	calcium phosphate nanoparticles
CEA	carcinoembryonic antigen

Commentary to:

Tissue Specific Expression of Suicide Genes Delivered by Nanoparticles Inhibits Gastric Carcinoma Growth

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The global statistics regarding incidences of and deaths from gastric cancer are staggering: it has accounted for as many as 650,000 deaths per year,[1] and among cancer-related deaths, it ranks as the second leading cause, behind only lung cancer.[2,3] Five-year survival rates hover around a meager 20% since traditional chemotherapies such as 5-fluorouracil (5-FU) and doxorubicin do not exhibit sufficient therapeutic properties in advanced-stages, often when a majority of cases are diagnosed.[1] Based on these dire statistics, it is obvious that new therapies must be developed to combat this disease, and one emerging approach is targeted suicide gene therapy.

Suicide gene therapy, where nonmammalian genes convert normally nontoxic prodrugs into toxic forms, is a promising form of therapy that is now in Phase I clinical trials for the treatment of prostate and colorectal cancer.[4,5] Bacterial cytosine deaminase (bCD) and herpes simplex type 1 thymidine kinase (HSV-1 TK) are two suicide genes known for their ability to convert nontoxic 5-fluorocytosine into toxic 5-FU and nontoxic ganciclovir (GCV) into toxic phosphorylated GCV, respectively. The resulting metabolites are integrated into the DNA and RNA of cells, leading to strand termination and eventual cell death.[6] While bCD is capable of acting as a suicide gene, it has been reported that yeast CD (yCD) is much more powerful in this regard.[7,8] Recently, a novel fusion suicide gene was developed consisting of both yCD and HSV-1 TK, termed yCDglyTK; when expressed in tumor cells, it performed prodrug conversion while rendering the cells more sensitive to radiation therapy.[6]

Gene therapy is, of course, most effective when delivery is both efficient and safe, especially when dealing with cancer. However, it has often proven difficult to find a balance between efficiency and safety. For example, viral vectors, which encompass some of the most common methods used in gene therapy due to their superior transfection efficiency, often induce an immune response[9] and can even cause patient death.[10] As a result, much recent work has been devoted to non-viral delivery methods, including cationic liposomes and calcium phosphate nanoparticles (CPNP). While cationic liposomes show potential regarding transfection efficiency and the size of DNA they can deliver, they can be toxic under certain conditions.[11] Conversely, Liu et al have recently shown that positively charged CPNP can also bind negatively charged DNA effectively, and these complexes are able to enter the cell to deliver the DNA with minimal toxicity.[12]

While efficient delivery of suicide genes is an attractive approach to treating gastric cancer, lack of tumor specificity can still lead to undesirable side effects. Preferably, the suicide genes would affect only malignant cells, while sparing normal, healthy cells. As many cancers, namely gastric, colon, breast and ovarian, overexpress the carcinoembryonic antigen (CEA) protein [reviewed in Ref. 13] it has come to light that selective therapy for colorectal cancer can be achieved using a CEA promoter that drives the expression of either bCD[14] or yCD.[15] In the December 2006 issue of Cancer Biology and Therapy, Liu et al describe a method of efficiently and selectively delivering the yCDglyTK suicide gene by placing it under the control of a CMV-enhanced CEA promoter (CV) and complexing it with CPNP. The group envisioned that once the genes were efficiently transferred via the CPNP, only cells expressing CEA, e.g., gastric cancer cells, would undergo cytotoxic effects after 5-FC was administered and subsequently converted to 5-FU.

The authors report that in CV-yCDglyTK-positive SGC7901 gastric cancer cells (CEA positive) cell viability was only 10.2%, while in CV-yCDglyTK-positive Hela cells (CEA negative) viability was 98% following the administration of 5-FC. When CPNP were used to deliver the suicide gene, SGC7901 cells exhibited only 25.36% viability, demonstrating the efficiency of CPNP delivery. Intriguingly, when stably transfected CV-yCDglyTK SGC7901 cells were mixed with untransfected SGC7901 cells, a significant "bystander effect" occurred after five days of treatment with 5-FC. Cell death was as high as 38.5% even when only 5% of the cells in the mixture were CV-yCDglyTK positive. In vivo

studies further confirmed the therapeutic potential of combining suicide genes with non-viral CPNP delivery vehicles. SGC7901 xenografts that received CPNP-CV-yCDglyTK injections showed marked tumor regression as compared to the untransfected control group, when both groups were treated with 5-FC.

Collectively, these results indicate that this novel, targeted system shows promise regarding the development of therapies for gastric cancers, or other malignancies that overexpress the CEA antigen. Since bCDglyTK and yCDglyTK fusion gene therapies have both been found to leave malignancies more susceptible to radiation therapy,[10,16,17] a natural next step for this group could be to utilize 5-FC, GCV and radiopharmaceuticals to investigate the possibility of synergistic and/or radiosensitization effects within their novel targeted system.

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