Chemists using light-activated molecules to kill cancer cells

August 8 2007

A key challenge facing doctors as they treat patients suffering from cancer or other diseases resulting from genetic mutations is that the drugs at their disposal often don't discriminate between healthy cells and dangerous ones -- think of the brute-force approach of chemotherapy, for instance. To address this challenge, Florida State University researchers are investigating techniques for using certain molecules that, when exposed to light, will kill only the harmful cells.

Igor V. Alabugin is an associate professor of chemistry and biochemistry at FSU. He specializes in a branch of chemistry known as photochemistry, in which the interactions between atoms, small molecules and light are analyzed.

"When one of the two strands of our cellular DNA is broken, intricate cell machinery is mobilized to repair the damage," he said. "Only because this process is efficient can humans function in an environment full of ultraviolet irradiation, heavy metals and other factors that constantly damage our cells."

However, a cell that sustains so much damage that both DNA strands are broken at the same time eventually will commit suicide -- a process known as apoptosis.

"In our research, we're working on ways to induce apoptosis in cancer cells -- or any cells that have harmful genetic mutations -- by damaging both of their DNA strands," Alabugin said. "We have found that a group

of cancer-killing molecules known as lysine conjugates can identify a damaged spot, or 'cleavage,' in a single strand of DNA and then induce cleavage on the DNA strand opposite the damage site. This 'double cleavage' of the DNA is very difficult for the cell to repair and typically leads to apoptosis."

What's more, the lysine conjugates' cancer-killing properties are manifested only when they are exposed to certain types of light, thus allowing researchers to activate them at exactly the right place and time, when their concentration is high inside of the cancer cells, Alabugin said.

"So, for example, doctors treating a patient with an esophageal tumor might first inject the tumor with a drug containing lysine conjugates," he said. "Then they would insert a fiber-optic scope down the patient's throat to shine light on the affected area." The light exposure would activate the drug, leading to double-strand DNA damage in the cancerous cells -- and cell death -- for as much as 25 percent to 30 percent of the cells in the tumor,at a rate that rivals in efficiency any of the highly complex and rare DNA-cleaving molecules produced by nature, Alabugin said -- and, perhaps just as importantly, avoids damage to healthy cells.

For tumors located deeper within the body, he pointed to other studies showing that a pulsed laser device can be used to penetrate muscle and other tissues, thereby activating the drugs using near-infrared beams of light.

As proof of principle to the idea that lysine conjugates possess anti-cancer activity, Alabugin collaborated with cancer biologist Dr. John A. Copland of the Mayo Clinic College of Medicine in Jacksonville, Fla. In their tests, several of the molecules demonstrated little effect upon cultured cancer cells -- in this case, metastatic human kidney cancer cells -- without light, but upon phototherapy activation killed more than 90

percent of the cancer cells with a single treatment. Future work will include demonstrating anti-cancer activity in an animal model. Successful completion of the preclinical studies then could lead to clinical trials with human patients.

Citation: "DNA Damage-Site Recognition by Lysine Conjugates," was published in the July 23 issue of the *Proceedings of the National Academy of Sciences*.

Source: Florida State University