Scientists design a PSA-activated protoxin that kills prostate cancer

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Scientists have found a way of using a protein made by prostate cancer to target and kill the cancer cells themselves. In preliminary studies the new therapy affected only the prostate, without causing damage to other healthy tissues, and now it is being tested in a phase I clinical trial.

Prostate cancer is one of the commonest cancers in men, with nearly 680,000 new cases each year worldwide and more than 220,000 deaths. Furthermore, by the age of 80, approximately 80% of all men will have developed a non-cancerous condition called benign prostatic hyperplasia (BPH) in which the prostate gland becomes enlarged. The findings reported today (Friday 10 November) have the potential to improve the survival and quality of life for men suffering from both these conditions.

Sam Denmeade, associate professor of oncology at John Hopkins University, USA, reported to the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Prague that he and his team3 had developed a protoxin, named PRX302, by modifying an inactive molecule, proaerolysin (PA). They engineered PRX302 to be activated by prostate-specific antigen (PSA) – a protein made in higher than normal levels by prostate cancer. Once activated, they hoped that it would target and kill prostate cancer cells specifically.

He explained: "This represents a different kind of 'targeted' therapy, in that it seeks to use a protein made by the cancer to destroy itself."

Initial tests in the lab and in animals revealed that when the protoxin was

injected into cancerous prostate tissue, it had a significant effect. "In the lab, PRX302 produced significant and often complete regression of the prostate cancer. Since the PSA gene is only found in primates and humans, we then injected either 0.35 or 4.1 micrograms as a single 25 microlitre injection into PSA-producing prostates of cynomolgus monkeys where it resulted in destruction of either 25 or 50% of prostate tissue respectively. This extensive damage was confined to the prostate with no toxicity observed in any other normal tissues, including those adjacent to the prostate such as the bladder, urethra, rectum and seminal vesicles. Furthermore, two weeks after the injection, we saw a disappearance of the toxin, but the continued presence of dead tissue, suggesting that the toxin's effects could be long lasting.

"Our observations suggest that injections into the prostate of this engineered, PSA-activated protoxin might have potential in treating men with locally recurrent or advanced prostate cancer, or for those with BPH where the protoxin could be used to reduce the size of the enlarged prostate," said Professor Denmeade. "A phase I clinical trial is in progress now for men with locally recurrent prostate cancer after definitive radiation therapy."

At the moment, the therapy involves injecting the protoxin directly into the prostate. "As such, its application is limited to men with recurrent disease after radiation who still have prostates. If it were to work very well it might be used earlier, in combination with other treatments, most likely radiation. In addition, the toxin is also under consideration as treatment for BPH. We hope that we will be able to further modify the toxin to make a systemic form that could be used to treat advanced prostate cancer in the future."

The study is treating the third cohort of patients and interim results are expected to be available at the end of the year.

PA is an inactive precursor of a bacterial protein that kills cells by forming large pores in the cell membrane. PRX302 kills the cancer cells in the same way when activated by PSA. The idea for this approach to treating prostate cancer came when Prof Denmeade, who had been working for some time on ways to harness the activity of PSA with drugs, heard about PA. "We called Dr Buckley, who is the world expert on PA, and discussed our strategy. Within two weeks he had generated the toxin and then we tested it for toxicities against a variety of cancers in our lab before starting our studies in prostate cancer."

Source: European Organisation for Research and Treatment of Cancer