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A 'bioreactor' for bladder cancer cells

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Finding a molecular therapy that can bypass the bladder's natural defenses against bacteria and viruses to kill cancer cells on the organ wall isn't easy. But researchers at The University of Texas M.D. Anderson Cancer Center (http://www.mdanderson.org/) appear to have made a breakthrough. An adenovirus expressing high and sustained levels of the anti-cancer agent interferon-α (INF-α) together with a gene-transfer-enhancing agent, has resulted in a 'remarkable' regression of tumors with little to no toxicity, says William Benedict, Professor of Cancer Medicine in the Department of Genitourinary Medical Oncology (Figure 1).

Recurrence common

Bladder cancer, the fourth most common cancer in men and the tenth most common in women, remains an important medical problem. It leads to the death of about 30,000 people in the United States and Europe each year. 'Most people don't die from bladder cancer right away, but it occurs repeatedly throughout the course of their lifetime,' explains Michael A. O'Donnell, Associate Professor and Chief of Urologic Oncology at the University of Iowa College of Medicine (http://www.medicine.uiowa.edu). 'Every time it comes back it's harder to treat.'

The current therapy begins with surgery, transurethral resection (TUR), to remove tumors from the bladder wall [1]. But 60–70% of superficial tumors come back. Because of the high recurrence rate, the use of chemotherapy or Bacillus Calmette-Guerin (BCG) therapy–a biologic that is about twice as effective as chemotherapy in the bladder–has become widespread, says O'Donnell. Still, a majority of patients eventually relapse and many die from metastatic bladder cancer.

Gene therapy has long been proposed as an effective treatment for bladder cancer. Because the bladder is a self-contained system, the safety concerns raised by the systemic administration of gene therapy vectors are not thought to be an issue. The challenge, however, lies in devising a way for the virus to get through the watertight glycosaminoglycan or GAG layer that functions 'to keep bugs out,' says Benedict.

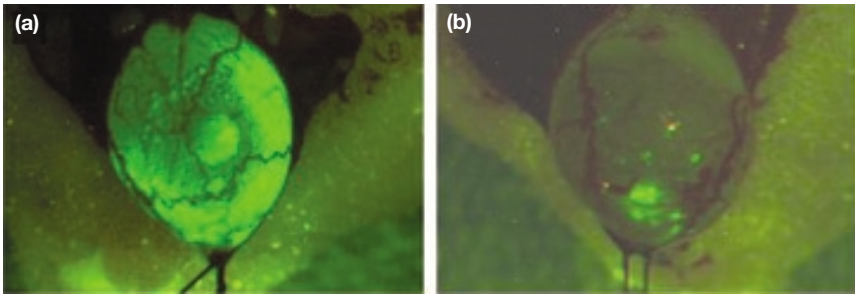

Figure 1. Treatment of a mouse bladder tumor **(a)** with Ad-INF-α/Syn3 **(b)** causes significant tumor regression in mouse models, as visualized with green fluorescent protein. Image courtesy of W. Benedict of The University of Texas M.D. Anderson Cancer Center (http://www.mdanderson.org/).

An interferon bioreactor

A superficial bladder cancer model was developed by instilling human cancer cells expressing a green fluorescent protein in mouse bladders, which also enables tumor visualization [2,3]. These tumors were then treated using recombinant adenoviruses (Ad- INF-α), engineered to produce high levels of INF-α but unable to replicate, and Syn3, an agent that enables adenoviruses to enter cells lacking the receptor usually required for binding [4]. '[Syn3] takes the GAG layer off but it does other things as well,' says Benedict of this proprietary molecule developed by Canji, a biotechnology company affiliated with Schering-Plough Corp. (http://www.sch-plough.com).

Although interferon has clinic utility as an 'enhancing' immunostimulant when used in combination with BCG therapy, this new approach resulted in protein levels that were about tenfold higher than achieved with instillations without it [1,5]. Also, the INF-α expression lasted more than a week, as compared to the short time people are able to retain the protein in the bladder as part of the conventional treatment. 'We're making a lot of interferon locally for a long period of time in the normal and adjacent tumor cells,' says Benedict. 'We call it a bioreactor.'

Mice not men

The gene therapy had a 'pretty phenomenal effect on the bladder cancers,' says O'Donnell, who was not involved with the research. 'It provides a strong basis for clinical trials.' Further, the treatment affected tumor cells known to be resistant to the interferon protein and achieved these results with

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'very little toxicity,' says Benedict. 'The Ad-interferon [appears to be] a different drug than interferon protein. It is interferon but it's more than interferon.' Although this could lead to a treatment for superficial bladder and other cancers, 'all this is qualified,' says O'Donnell. 'We can do really well curing mice of their cancer. It seems to be a lot more complicated with people.'

References

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The fight against cancer: the next round

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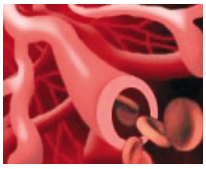

It has now been almost three decades since it was first proposed that inhibition of angiogenesis (the formation of new blood vessels) could play a crucial role in the treatment of cancer. However, it has taken quite some time for 'anti-angiogenesis' drugs to become a reality within the clinical setting, and despite early enthusiasm, they have failed to make a dramatic impact in clinical trials. In Phase III trials that have been conducted to date, these drugs have not resulted in significant increases in survival rates, and toxicity within the patient remains an issue. Scientists at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (http://www.hopkinskimmelcancercenter.org/) have shown that combining two different types of drugs in a 'one-two punch' type of therapy might be more effective in the treatment of cancer than single agents [1].

The armamentarium

Angiogenesis plays a pivotal role in tumor growth, invasion and metastasis. Normal endothelial cells are usually quiescent, dividing approximately every seven years. However, in malignant cells accelerated growth occurs, with cells sometimes dividing as often as once per week. Up until this point of accelerated growth commences, it is usually genetic and epigenetic alterations that are responsible for deregulated tumor growth.

However, beyond a certain size tumors require certain nutrients and oxygen to grow; signaling between various growth factors and endothelial receptors is responsible for endothelial cell survival, proliferation, differentiation and angiogenesis, which are necessary to allow this growth to take place. As a result, many researchers have focused on vascular endothelial growth factors (VEGF) and corresponding receptors as targets for anti-angiogenesis therapy.

The interaction that takes place between VEGF and its receptors activates receptor-associated kinase activity and crucial signaling pathways that lead to tumor angiogenesis. One such drug that has been clinically developed is designated PTK787/ZK222584; this agent selectively and potently inhibits the VEGF receptor tyrosine kinase and has previously been shown to inhibit VEGF-mediated angiogenesis in phase I studies [2].

The one-two punch

Roberto Pili and his colleagues at the Johns Hopkins Kimmel Cancer Center applied a combination approach to target tumor growth and angiogenesis by using both PTK787/ZK222584 and a histone deacetylase (HDAC) inhibitor, designated NVP-LAQ824, in mouse and cell-line models [1]. 'Combining these two types of drugs may have a greater impact on cancer development than using them alone,' says Roberto Pili. 'Our idea is to attack the way cancers form new blood vessels by disrupting the angiogenesis process in two different cells.'

HDAC inhibitors represent a class of therapeutic agents that act against tumors through chromatin remodeling and modulation of gene expression, thereby affecting the cell cycle and survival pathways. During tumor development, acetyl groups are removed from histones, forcing the DNA to remain tightly coiled and restricting gene activation. HDAC

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