CANCER VACCINES

Double-dipping DNA vaccine

Vaccines and agents that target the tumour vasculature are two of the most attractive approaches to treating cancer. The heat-shock protein calreticulin (CRT) has been shown to combine the best of both worlds, having both immunogenic and anti-angiogenic effects. In the September issue of *The Journal of Clinical Investigation*, Wen-Fang Cheng *et al.* report that this dual-function molecule prevents tumour growth in mice.

CRT is a Ca^{2+}-binding protein of the endoplasmic reticulum that facilitates MHC class I antigen processing. When coupled to tumour antigen, CRT enhances the cytotoxic T-cell response against tumours, indicating its potential to increase vaccine efficiency. Remarkably, CRT has also been reported to be an endothelial-cell inhibitor that prevents angiogenesis and tumour development.

But does this protein have any effect on tumour growth *in vivo*? To test this, Cheng *et al.* created a DNA vaccine that linked the gene that encodes CRT to that of the human papillomavirus oncoprotein E7. Vaccination of mice with DNA that encodes the CRT–E7 fusion significantly enhanced the E7-specific cytotoxic T-cell response, and also induced production of antibodies against the antigen. Furthermore, CRT–E7 protected mice against the E7-expressing tumour cell line TC-1 when mice were immunized either before or after tumour development. Fusion of CRT to E7 was required for immunity, as CRT DNA that was simply mixed with E7 DNA did not enhance E7 immunogenicity.

Did the therapeutic effect of the CRT-containing construct arise from its immune-activating function, or from its anti-angiogenic function? The authors examined the effects of CRT/E7 vaccination in mice that were depleted of both cytotoxic and helper T cells. These mice were still protected from tumour growth, indicating that CRT can act independently of T cells. Furthermore, examination of pulmonary tumours grown in the mice revealed a reduction in microvessel density after CRT treatment, indicating a reduction in tumour angiogenesis.

The vaccine, however, was not as effective in immunodepleted mice as it was in immunocompetent ones, indicating that a combination of the immunological and antiangiogenic functions of CRT is required to generate the most potent antitumour effect. In the future, this approach might be applied to other cancer systems, as CRT could be linked to other known tumour antigens to increase their immunogenicity, as well as reduce tumour angiogenesis.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Cheng, W.-F. *et al.* Tumor-specific immunity and antiangiogenesis generated by a DNA vaccine encoding calreticulin linked to a tumor antigen. *J. Clin. Invest.* **108**, 669–678 (2001)

FURTHER READING Michalak, M. *et al.* Calreticulin: one protein, one gene, many functions. *Biochem. J.* **344**, 281–292 (1999)

WEB SITE

T. C. Wu's lab: www.hopkinsmedicine.org/graduateprograms/immunology/faculty/wu.html

IN BRIEF

THERAPEUTICS

A combinatorial approach for selectively inducing programmed cell death in human pancreatic cancer cells.

Su, Z. et al. Proc. Natl Acad. Sci. USA **98**, 10332–10337 (2001)

Pancreatic cancer is one of the leading causes of cancer death, and one of the most difficult to treat, but a new strategy that combines two independent treatments — expression of *MDA7* and antisense antibodies that target the oncogene *KRAS* — is now showing promise. Pancreatic cells are resistant to *MDA7* expression, which induces growth arrest and apoptosis in other tumour types. However, *KRAS* antisense treatment sensitizes cells to *MDA7* expression, and apoptosis ensues through upregulation of *BAX*.

DIAGNOSTICS

Bioassay of prostate-specific antigen (PSA) using microcantilevers.

Wu, G. *et al. Nature Biotechnol.* **19**, 856–860 (2001)

A great challenge to diagnostics is high-throughput, quantitative protein detection. Wu and colleagues have used microcantilevers — tiny platforms that deform when proteins bind — to detect prostate-specific antigen (PSA), a marker for prostate cancer. Coating the microcantilever surface with antibodies to PSA allows wide ranges of unlabelled PSA to be detected in high concentrations of serum proteins. The technique could be applied to any protein, and lends itself to detecting many different proteins in parallel.

GENE THERAPY

A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumours in combination with doxorubicin.

Li, Y. *et al. Cancer Res.* **6**, 6128–6136 (2001)

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death. α-Fetoprotein (AFP), a tumour marker used to diagnose this cancer, is expressed by HCCs but rarely by normal hepatocytes. Using the AFP transcriptional regulatory element to control expression of an oncolytic adenovirus, the authors created a vector — CV890 — to specifically target HCC cells. CV890 only replicated in and destroyed AFP-producing HCC cells, and reduced the growth of HCC in mice. Combination of CV890 with doxorubicin demonstrated synergistic antitumour efficacy. These findings support the development of this oncolytic vector for treating HCC.

ANIMAL MODELS

HV_{MNE}, a novel lymphocryptovirus related to Epstein–Barr virus, induces lymphoma in New Zealand White rabbits.

Ferrari, M. G. *et al. Blood* **98** (in the press)

DNA viruses such as Epstein–Barr virus (EBV) have long been associated with B-cell cancers. They have also been reported to cause T-cell malignancies, but their role in tumorigenesis remains controversial. HV_{MNE} is a novel EBV-like virus isolated from macaques with a T-cell lymphoma. The authors show that this virus causes malignant T-cell lymphoma in New Zealand White rabbits. T cells from the animals were found to carry viral DNA, acquire interleukin-2 independence and constitutively activate the JAK/STAT pathway. This is a valuable new T-cell lymphoma animal model.

© 2001 Macmillan Magazines Ltd