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METASTASIS

CAR problems

Adenovirus-based gene therapy is being developed to treat late-stage and androgen-independent prostate cancer. Efficient adenovirus infection, however, depends on target-cell expression of the coxsackie adenovirus cell-surface receptor (CAR), which is required for adenovirus attachment to the cell membrane. By examining CAR expression levels in various tissue samples, Frank McCormick's group report that adenoviral gene therapy is likely to be most effective in treating prostate tumours after they have already become metastatic.

Several adenovirus-based gene-therapy protocols are being evaluated, at present, in prostate cancer clinical trials. Patients enrolled in these adenoviral trials, however, are being treated with virus, without evaluating the tumour expression levels of CAR. This has been a significant limitation in the evaluation and subsequent stratification of patients.

To determine which tumour types are most likely to respond to adenovirus gene therapy, McCormick's group developed a polyclonal antibody to human CAR and compared the expression levels in paraffin-embedded normal prostate (n = 33), primary tumour (n = 129) and metastatic tumour (n = 10) samples. They observed that normal prostate tissue had intense membrane staining in all epithelial cells in the region of cell-cell contact, with equally strong luminal membrane staining of the prostatic secretory epithelium. CAR

expression decreased — in both intensity and percentage of cells stained — in both low-grade and advanced primary prostate tumours. But tumours that have metastasized to bone, liver and lymph nodes express high levels of CAR. So adenoviral vectors might be most useful in treating metastatic tumours.

But why would CAR be expressed in normal tissue, downregulated in prostate tumours and then upregulated again in metastases? This expression pattern is similar to that of E-cadherin — a transmembrane glycoprotein that is involved in mediating cell-cell interactions and the differentiated epithelial phenotype. E-cadherin is strongly expressed in normal prostate epithelium and, like CAR, is localized to the lateral aspects of the cell, where cell-cell contact occurs. CAR expression seems to mirror the expression of E-cadherin, with a transient downregulation of E-cadherin in the primary tumour and a re-expression of the cell-surface molecule in metastases.

The authors propose that CAR might, like E-cadherin, function as a

tumour suppressor that is involved in cell adhesion. Transfection of CAR into the tumorigenic prostate cell line PC3 has been shown to inhibit tumour growth in mice. As proposed for E-cadherin, lack of expression of cell-adhesion molecules might promote the development of metastasis. Subsequently, metastatic tumour cells that can re-express cell-adhesion molecules, such as E-cadherin and CAR, might possess a survival advantage, allowing the cells to gain a foothold in a foreign environment. Further studies are required to determine the true function of CAR, but these findings reveal its potential as a gene-therapy target for metastatic tumours.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Rauen, K. A. *et al.* Expression of the coxsackie adenovirus receptor in normal prostate and in primary and metastatic prostate carcinoma: potential relevance to gene therapy. *Cancer Res.* **62**, 3812–3818 (2002)

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WEB SITE

Frank McCormick's lab:
<http://cc.ucsf.edu/mccormick/>