THERAPEUTICS

Stop signals

Trastuzumab (Herceptin) — a monoclonal antibody that targets the ERBB2 receptor — has achieved great success in treating breast cancer patients, but can this success be improved on? Mark Sliwkowski and colleagues, reporting in the August issue of *Cancer Cell*, have developed a new antibody that might do just that.

The limitation of trastuzumab is that it is only effective for women whose cancers overexpress *ERBB2*; however, the pathway is also activated in other cancers. ERBB2 acts as a coreceptor — it does not bind its own ligand — in the ERBB signalling pathway, so Sliwkowski and colleagues developed an anti-ERBB2 monoclonal antibody, 2C4, that was able to prevent the heregulin-induced binding of ERBB2 and ERBB3. 2C4 was also able to inhibit the activation of mitogen-activated protein kinase and AKT, two of the key downstream targets of the ERBB pathway.

But can 2C4 actually inhibit tumour growth? It was effective in cell lines and breast cancer xenograft models and, importantly, it was able to prevent growth in xenograft tumours that expressed low levels of *ERBB2*, for which trastuzumab was unsuccessful.

The ERBB pathway has also been implicated in the growth and survival of prostate cancer cells, and in their progression from an androgen-dependent to an androgen-independent state. Like trastuzumab, 2C4 was able to inhibit the growth of androgen-dependent prostate cancer xenografts. However, unlike trastuzumab, 2C4 was also effective against androgen-independent prostate cancer xenografts.

So, the 2C4 antibody shows great promise as a therapeutic agent against two different cancer types, one of which — androgen-independent prostate cancer — is particularly difficult to treat. A humanized version has already been developed and found equally effective. We await its clinical-trial results with great interest.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Agus, D. B. *et al*. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate cancer tumor growth. *Cancer Cell* **2**, 127–137 (2002)

FURTHER READING Baselga, J. A new anti-ErbB2 strategy in the treatment of cancer: prevention of ligand-dependent ErbB2 receptor heterodimerization. *Cancer Cell* **2**, 93–96 (2002)

WEB SITE

Mark Sliwkowski's lab: http://www.gene.com/gene/research/sciprofiles/molecularoncology/sliwkowski/index.jsp

IMMUNOLOGY

Presentation is everything

If information piles up and is not passed on to the right department, what are the chances that it will elicit a response or be acted on? Nil. Likewise, tumours might not actually lack tumour antigens but, if these antigens are not presented effectively to the immune system, activation of the immune response is unlikely. In the 27 July issue of *The Lancet*, Laurence Zitvogel and co-workers report a new source of tumour antigens — exosomes in tumour ascites — that enable loading of antigen-presenting cells, dendritic cells (DCs), to activate cytotoxic T cells and elicit an immune response against tumours, even if the tumours themselves are poorly immunogenic.

Tumour-derived exosomes are small vesicles that carry molecules that are involved in antigen presentation, such as MHC class I molecules, heat-shock proteins, tetraspanins and tumour antigens. Zitvogel *et al*. have previously shown that exosomes derived in cell culture are immunogenic; the present study indicates that exosomes can also be isolated in large quantities from tumour ascites from patients and that these are also immunogenic. For instance, monocyte-derived DCs loaded with ascitis exosomes from a patient with Mart1-positive melanoma induce differentiation and expansion of tumour-specific cytotoxic T cells that are derived from these patients, even if the tumours themselves are poorly immunogenic. The authors examined ascites from 10 other patients who had malignant effusions, and showed similar responses in ovarian and breast cancer in which the exosomes expressed *ERBB2* (also known as HER2/neu).

A comparison between primary tumour cell cultures and ascites showed that many more exosomes were harvested from ascitic fluids, and T-cell responses were easier to stimulate with exosomes from tumour ascites.

So how can this information be used further? Tumour-derived exosomes in ascites could be used to generate large numbers of tumour-specific T cells for adoptive immunity and could be used in vaccines. Whether exosomes will be clinically applicable for immunization against cancer, and whether they will help identify tumour antigens, are questions that are yet to be answered.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Andre, F. *et al*. Malignant effusions and immunogenic tumour-derived exosomes. *Lancet* **360**, 295–305 (2002)

FURTHER READING Ronchese, F. *et al.* Tumour antigens on tap. *Lancet* **360**, 268 (2002) | Thiery, C. *et al*. Exosomes: composition, biogenesis and function. *Nature Rev. Immunol.* **2**, 569–579 (2002)