IMMUNOTHERAPY

Self-improvement

Managing metastatic disease remains a crucial goal for cancer research. The use of immunotherapy against metastases is promising in principle, yet finding tumour-specific antigens is time consuming and not always fruitful. In their *Nature Biotechnology* paper, Richard Vile and colleagues report a novel immunotherapy-based approach to targeting metastatic melanoma through inducing an inflammatory response to self-antigens expressed in normal melanocytes.

Vile and co-workers used a plasmid expressing herpes simplex virus thymidine kinase under the control of the tyrosinase promoter, which is only active in proliferating melanocytes. When expressed in cells, thymidine kinase converts a systemically administered prodrug, ganciclovir, to its DNA-damaging triphosphate form, resulting in cell death. In theory, the death of the normal melanocytes will release antigens that, following presentation to T-cells, will result in the targeting of the malignant melanoma cells. One caveat of this is that producing T-cells that recognize self-antigens runs the risk of generating an autoimmune response as well.

Mice injected with plasmid into the opposite flank to that previously injected with B-16 malignant melanoma cells showed only transient inhibition of disease progression in the presence of ganciclovir. The efficacy of the immune response was improved by including a plasmid expressing high levels of heat-shock protein 70, which can make the presentation of self-antigens by dendritic cells highly immunostimulatory to T-cells. In addition, the number of treatments was increased from one to three. These changes effectively cured the mice of metastatic melanoma.

But what is the nature of the immune response in the cured mice? The authors showed that vaccination recruits CD8⁺ cytotoxic T-cells but, importantly, the CD8⁺ response is not

sustained, as cured mice cannot reject a subsequent challenge with B-16 cells, showing that memory T-cells are not produced. CD8⁺ T-cells are subject to tight controls to minimize the recognition of self, in part through the actions of regulatory CD25⁺ T-cells, the activation of which might prevent the establishment of self-recognizing memory cells. So, the authors used the same regimen to treat CD25⁺ T-cell-depleted mice and saw some establishment of immunological memory and cure of 80% of animals after only one round of treatment. Therefore, CD25⁺ T-cells might well regulate the effectiveness of this therapy.

The authors conclude that for their novel immunotherapy strategy to work efficiently against metastases, activation of regulatory T-cells needs to be controlled, allowing a more effective response and the production of long-term memory T-cells. However, reducing the numbers of CD25⁺ T-cells could increase the development of autoimmune disease, which was evident in the treated mice, but was not an overt clinical problem. Therefore, targeting self-antigens to treat tumours in humans will require careful modulation of an autoimmune response.

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References and links

ORIGINAL RESEARCH PAPERS Daniels, G. A. A simple method to cure established tumours by inflammatory killing of normal cells. *Nature Biotechnol.* 1st Aug 2004 (doi:10.1038/nbt999)

TRIAL WATCH

Taking a slug at cancer

A Phase II trial of kahalalide F, an agent isolated from the sea slug *Elysia rufescens*, has been initiated for the treatment of patients with non-small-cell lung cancer (NSCLC), and another is underway for treatment of patients with melanoma. The drug, which is a depsipeptide currently under development by PharmaMar (Madrid, Spain), has been shown to have a novel mechanism of action — it disrupts the lysosomal membrane of cells, inducing necrosis specifically in tumour cells. Other studies have shown that the drug is able to inhibit expression of transforming growth factor- α , block epidermal growth factor signalling pathways and induce non-p53-mediated apoptosis. A previous Phase I study showed promising results — the drug had a favourable safety profile and was not reported to cause alopecia, mucositis, renal or haematological toxicities in patients. One Phase II trial will be a multicentre open-label study in 25 patients with NSCLC who have relapsed or progressed after first-line chemotherapy. Another Phase II trial will also be an open-label study that will include 18 patients with melanoma. Both trials will be performed at 12 European centres and tumour response will be used as the primary end point. The studies will also evaluate the pharmacokinetics of kahalalide F as well as additional aspects of drug safety. Additionally, kahalalide F is in Phase II clinical trials for the treatment of hepatocellular carcinoma.

WEB SITE

Kahalalide F: <http://www.pharmamar.com/en/pipeline/kahalalide.cfm>

Profiling ALL drug resistance

A microarray analysis study has identified gene-expression patterns associated with resistance to therapy in patients with acute lymphoblastic leukaemia (ALL). William Evans and colleagues assessed the expression profiles of 14,500 genes in primary B-linkage leukaemia cells isolated from 173 children with ALL. Specific profiles were associated with cells that were resistant to prednisolone, vincristine, asparaginase or daunorubicin — drugs commonly used to treat this type of cancer. The authors then showed that these profiles could be used to predict which of these patients would become resistant to each of these drugs, as well as an independent population of patients treated with the same medications. Remarkably, only 124 genes were associated with a lack of response to these therapies, and 121 of these genes had not been previously found to have a role in drug resistance. These findings reveal previously unrecognized targets for improving the efficacy of chemotherapy in patients with ALL — this is an important advance, as 20% of these patients do not respond to therapy.

ORIGINAL RESEARCH PAPER Holleman, A. *et al.* Gene-expression patterns in drug-resistant acute lymphoblastic leukemia cells and response to treatment. *N. Engl. J. Med.* 351, 533–542 (2004)