Breakthrough antibody therapy for lethal cancer

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Researchers from the Mayo Clinic in Rochester, MI, USA (http://www.mayoclinic.org/rochester/) have created an anti-tumour immune response towards malignant melanoma, one of the most lethal forms of skin cancer, where none exists in nature [1].

The team introduced an antibody called sHIgM12 into mice. This antibody crosslinks structures on the surface of dendritic cells, the key players in initiating select immune responses, with structures on the surface of T-cells. This crosslinking results in the activation of the T-cells, invoking an immune response. Under normal circumstances dendritic cells do not respond to malignant melanoma, that is, the cancer is said to be poorly immunogenic. By introducing the antibody therapy the team observed a consistently strong – and often curative – therapeutic effect.

Prophylactic potential

To investigate the prophylactic potential of the therapy, the team took one group of mice and treated them with the experimental sHIgM12 antibody. Two control groups were treated with known antibodies that do not prompt crosslinking structures. Malignant melanomas were then transplanted into all the mice from the three different groups.

Less than 4% of the mice were tumour free in the two control groups. By contrast, 69% were tumour free in the group receiving the experimental antibody treatment. In addition, the few mice in this group that did develop tumours experienced significantly inhibited tumour growth compared with controls.

In an attempt to model what happens during lung metastasis, another group of mice received intravenous transplants of tumours that seeded their lungs with dozens of discrete foci of melanoma. After three days, some of these animals were treated with the sHIgM12 antibody or a control antibody. Of the animals that received the crosslinking antibody treatments, 48% were tumour free 3–4 weeks after tumour engraftment. The remaining 52% developed substantially fewer tumours relative to the animals receiving the control antibody, showing that the crosslinking antibody had a strong treatment effect, even when animals were not completely cured. In contrast, all the mice that received control antibodies developed large numbers of tumours in their lungs.

Potentiating dendritic cells

Sunil Chatterjee, a Research Professor at the Case Western University Department of Internal Medicine, Cleveland, OH, USA (http://intmed.uc.edu/), who specializes in using immunotherapy to treat malignancies, commented that; 'Although the anti-tumour effect of this approach is partial, this *in vivo* manipulation of dendritic cell is more practical for clinical use than the conventional immunotherapy using *ex vivo* treated, autologous dendritic cells for cancer patients. The "crosslinking" antibody can be used for all patients, and is not patient specific.'

The authors propose that the sHIgM12 crosslinking antibody binds to dendritic cells, potentiating their ability to activate naïve T cells, which in turn promotes a protective response against an otherwise poorly immunogenic target.

In the USA alone, malignant melanoma is diagnosed in approximately 50,000 people and claims the lives of 7000 people every year. If effective in humans, the sHIgM12 antibody could prove to be a powerful weapon against this form of cancer, without the toxic side effects of either chemotherapy or radiation. Larry Pease, Professor of Immunology at the Mayo Clinic College of Medicine, and one of the co-authors of the paper, said that 'this therapeutic strategy, still in its experimental stages, seeks to alter the immune response by modifying the function of central regulatory cells. Similar approaches might be useful for altering the immune response in a variety of diseases that have an immune basis.'

Reference

1 Radhakrishnan, S. *et al.* (2004) Immunotherapeutic potential of B7-DC (PD-L2) crosslinking antibody in conferring antitumor immunity *Cancer Res.* 64, 4965–4972

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