Nature Reviews Cancer | AOP, published online 14 September 2006; doi:10.1038/nrc1995

VACCINES

Everything in moderation

DOI:
10.1038/nrc1995

URLs
IFNγ
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=3458

Tumour vaccines aim to elicit potent immunity against a tumour, but one obstacle that they must overcome is the poor reactivity of T cells for tumour-associated antigens (TAAs). Mimotopes are mimics of tumour epitopes that can be used in vaccines to increase the number and function of TAA-specific T cells, but tumour regression in patients often does not correlate with the magnitude of the T-cell responses that are caused. Jill Slansky and colleagues have now shown that it is not the peptides that bind with highest affinity to the T-cell receptors (TCRs) that stimulate the most effective anti-tumour response, but those that bind with moderate affinity.

The authors identified six mimotopes from a combinatorial peptide library that, when complexed with the major histocompatibility complex molecule H-2L^{d}, increased affinities for a representative TCR that recognizes the AH1 T-cell epitope from a mouse colon tumour. All six mimotopes stimulated the production of interferon-γ (IFNγ), which is a potent activator of macrophages and is crucial for an effective response against solid tumours, from a T-cell clone in cell culture. They also all showed a correlation between their binding affinity to the TCR and their functional stimulation of the T cells.

So, does this correlation between binding affinity and functional stimulation hold *in vivo*? Mice were first vaccinated with mimotopes and then challenged with colon tumour cells. The AH1 peptide provided no protection from tumour growth, as expected. Unexpectedly, however, the intermediate-affinity mimotopes were most effective — a significant number of mice remained tumour free for more than 60 days compared with mice vaccinated with high-affinity mimotopes. When the high-affinity peptides were examined further, Slansky and colleagues found that although numbers of AH1-specific T cells with the expected expression of activation markers were increased in the mice, these T cells had defects in effector function. Tumour-infiltrating T cells in the mice that were vaccinated with high-affinity mimotopes produced significantly less IFNγ than those in mice that were vaccinated with the intermediate-affinity mimotopes. Interestingly, this was specific to stimulation with the AH1 mimotopes, as treatment of the mice with other T-cell stimuli induced higher IFNγ production.

These data show that it is the quality and not the quantity of the T-cell response that determines the effectiveness of the immune response to these tumour vaccines *in vivo*. This should be taken into account when designing peptide vaccines for anticancer therapy in the future.

Ezzie Hutchinson

ORIGINAL RESEARCH PAPER McMahan, R. H. *et al.* Relating TCR-peptide-MHC affinity to immunogenecity for the design of tumour vaccines. *J. Clin. Invest.* **116**, 2543–2551 (2006)