IN THE NEWS

Hope for peanut allergy? A vaccine that can protect people from peanut allergies could be in clinical trials within a year, according to scientists from the Mount Sinai Medical School, New York.

It is estimated that ~1.5 million people in the United States alone suffer from potentially fatal allergies to peanuts, and at present there is no cure. Research now published in the *Journal of Allergy and Clinical Immunology* describes the development and testing in mice of a promising new vaccine.

In this study, led by Dr Hugh A. Sampson, a strain of *Escherichia coli* bacteria was developed that produced genetically modified forms of three peanut allergens. The proteins had been altered so that they could not be recognized by immunoglobulin E antibodies, and so no allergic reaction could occur in response to these proteins. The bacteria were heat killed and then administered as a suppository to mice with peanut allergies. The vaccine effectively protected mice from subsequent exposure to peanuts, even when this occurred 3 months after treatment.

According to Sampson, "This particular vaccine, which could be adapted for human use, provides some hope that we may be able to treat peanut allergy in human patients and that we will no longer see symptoms" (*Reuters*). Clinical trials are now required to test whether this vaccine will also be effective in humans.

Jenny Buckand

LYMPHOCYTE SIGNALLING

Contrasting genetic approaches find a role for CARD11

CARD11 (also known as CARMA1) — a member of the membrane-associated guanylate kinase (MAGUK) family of proteins — is essential for lymphocyte activation, as now shown by gene targeting and genome-wide mouse mutagenesis screens.

MAGUK proteins are involved in the assembly and clustering of receptors and intracellular signalling molecules at the neuronal synapse. Structural similarities between the synaptic junctions in neurons and lymphocytes, as well as findings from studies using cell lines, led Hara *et al.* to generate *Card11*$^{-/-}$ mice to investigate the role of this protein in lymphocyte signalling.

What effect did the absence of Card11 have on lymphocyte signalling? *Card11*$^{-/-}$ T cells showed impaired proliferation and reduced production of interleukin-2 after antigen-receptor stimulation, and failed to proliferate in response to activation of protein kinase C (PKC). *Card11*$^{-/-}$ B cells also showed defective proliferation and impaired cell-cycle progression after antigen-receptor stimulation. In addition, the proliferation of *Card11*$^{-/-}$ B cells in response to lipopolysaccharide (LPS) — the ligand for Toll-like receptor 4 (TLR4) — was reduced. So, Card11 seems to be required for the transduction of signals that are downstream of antigen receptors and TLRs.

Further examination of the signalling events in *Card11*$^{-/-}$ lymphocytes showed that the proliferation defects result from impairments in the activation of JUN N-terminal kinase (JNK) and nuclear factor-κB (NF-κB) signalling pathways, and confirmed that Card11 functions downstream of PKC activation. Finally, the authors tested the response of *Card11*$^{-/-}$ mice to T-cell-dependent and -independent antigens, and showed that Card11 is required for the activation of mature T and B cells *in vivo*.

Using the chemical mutagen ethylnitrosourea (ENU), Jun *et al.* generated a library of random, genome-wide point mutations to try to identify regulators of immune responses. Amongst others, they derived a mutant mouse strain, termed *unmodulated*, in which high levels of cell-surface IgM antigen receptors are expressed by circulating IgD^{+} B cells. Mapping and sequencing experiments showed that the phenotype resulted from a point mutation in the coiled-coil (CC) domain of *Card11*, which is thought to destroy the structure of the CC domain, but the mutated Card11 protein is expressed at normal levels.

B cells from *unmodulated* mice showed defective proliferation in response to antigen-receptor stimulation, but the response of these cells to LPS was normal. T-cell receptor (TCR)-mediated activation was also normal, but co-stimulation through CD28 was impaired. In agreement with the findings in the *Card11*$^{-/-}$ mice, the authors of this study found that the defective B-cell proliferative responses in the *unmodulated* mice resulted from impaired activation of JNK and NF-κB signalling pathways.

The levels of IgM and IgG3 in the sera of *unmodulated* mice were markedly reduced, which led Jun *et al.* to investigate B-cell antibody responses in these mice. Responses to both T-cell-dependent and -independent antigens were defective, with T helper 1 (T_H1)-cell responses being more severely affected than T_H2-cell responses. In addition, high levels of serum IgE developed with increasing age, resulting in spontaneous atopy in these mice. The authors concluded that Card11 has a crucial role in regulating humoral immunity and atopy.

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References and links

ORIGINAL RESEARCH PAPERS Jun, J. E. *et al.* Identifying the MAGUK protein Carma-1 as a central regulator of humoral immune responses and atopy by genome-wide mouse mutagenesis. *Immunity* **18**, 751–762 (2003) | Hara, H. *et al.* The MAGUK family protein CARD11 is essential for lymphocyte activation. *Immunity* **18**, 763–775 (2003)