maintenance of synapses,' said Herz. The synaptic loss is closely associated with AD and dementia, therefore, he believes that the interference of this process by ApoE4 might be involved in late-onset AD.

Future directions

But he suspects that the lipoprotein receptors will turn out to have other ligands as well. 'There are seven members of this gene family of receptors and all of them are expressed on neurons at some point during development, either throughout the brain or in specialized subsets,' he noted. 'We have identified a specific ligand, reelin for two of them, which means that the others most likely will have functional ligands which we simply do not know about.'

His goal is to identify them. 'We have a very strong lead on one of them,' he said. 'We are using mutants in which we have made very specific mutations in the receptors, which allows us to assess their role in the synapse. And from that we now have much more detailed information of how in the synapse ApoE receptors function in modulating neurotransmission.'

Cooper is excited by the prospect of a new ligand. 'If there is another compound out there which binds to these receptors and which alters neurotransmission, then people would certainly want to know about it,' he said. 'Sounds like we have to stay tuned.'

The work was presented at the 53rd annual meeting of the *American Society of Human Genetics* 4–8 November 2003 (http://www.ashg.org).

Single target's broad potential

Caroline Cross, BMN News

A novel treatment for flu that targets a marker expressed on recently activated T cells could be used to treat a host of immune mediated diseases, report UK researchers.

Excessive immune response

When mice infected with influenza A are treated with a protein that targets OX40, a costimulatory molecule expressed on recently activated T cells, the animals' flu symptoms disappear.

'In the lung you tend to see an immune response that far exceeds what is needed to clear the pathogen,' said team leader Tracy Hussell at Imperial College London, UK (http://www.ic.ac.uk), whose latest data are published in the *Journal of Experimental Medicine* [1]. It is this excessive immune response that causes symptoms such as coughing and wheezing.

Unlike other anti-inflammatory treatments, including corticosteroids that affect all T cells, the OX40 treatment only inhibits cells recently

activated with antigen. 'It specifically dampens down those cells that are responding at that time,' she said. If treatment is stopped while some cells remain in the lung, sufficient numbers enter the T cell memory pool to allow cellular immunity to develop.

Another advantage of the treatment is that it is not specific for a particular pathogen and so can be used to treat a range of inflammatory disorders.

Immunotherapy target

Andrew Weinberg, a researcher at the Providence Portland Medical Center in Oregon, USA (http://www.phsor.org), has shown that in animal models of autoimmunity, such as the mouse model of multiple sclerosis, so-called experimental autoimmune encephalomyelitis (EAE), downregulation of OX40 signalling blocks the initial waves of inflammation.

'We have shown that OX40 positive T cells are the autoantibody-specific T cells within the inflammatory lesions of EAE,' he said. Blocking OX40 signalling, or deleting OX40 positive cells, reduces the symptoms without affecting the rest of the T cell repertoire, he says.

And the versatility of this molecule as a target for immunotherapy does not stop with downregulation. Upregulating OX40 signalling can enhance desirable

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immune responses. Indeed, Weinberg thinks the greatest therapeutic potential for OX40 regulation could lie in cancer therapies.

'Our group and others have now shown that giving an agonist OX40 antibody to mice with tumours has profound proinflammatory effects leading to the eradication of tumours in several models,' he said. The treatment also increases the number of memory T cells, thereby enhancing antigen specific cellular immunity.

OX40 conservation

Fortunately, the OX40 molecule is highly conserved between mice and humans and both Hussell and Weinberg hope that OX40 technologies will reach the clinic soon. Plans are afoot to test it on healthy individuals and asthmatics – a group who could benefit greatly as viral infections exacerbate asthma.

However, Weinberg sounds a note of caution. 'Unfortunately, these recombinant fusion proteins are expensive to produce and therefore expensive for treatment,' he said. But, he added, 'If small molecules could be found to inhibit OX40 specifically, then you could possibly treat flu symptoms with a nasal spray and everyone could take advantage of this technology at a reasonable price.'

Reference

1 Humphreys, I.R. *et al.* (2003) A critical role for OX40 in T cell-mediated immunopathology during lung viral infection. *J. Exp. Med.* 198, 1237–1242

Making sense of gene therapy

Helen Dell, BMN News

Plans to repair, rather than replace, defective genes have taken a tentative step closer to the clinic, report US researchers who have used RNA enzymes to successfully repair the product of a disease gene in mammalian cells.

Repair versus replace

Repairing genetic instructions has 'significant advantages' over traditional gene therapy, which aims to replace faulty genes, says Bruce Sullenger, Professor of Surgery at Duke University School of Medicine in North Carolina, USA (http://www.duke.edu).

The problem with the traditional approach to gene therapy is that when a healthy gene is inserted to replace a defective version, it is inserted at random. This can cause problems because the gene loses much of its surrounding DNA, which contains regulatory information, and the replacement gene can also interfere with its new neighbours.

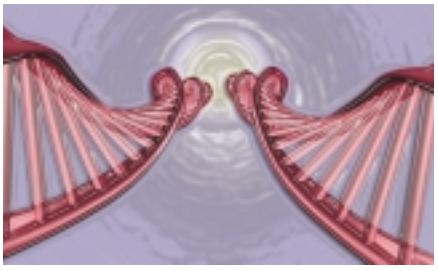
Sullenger likens gene therapy to correcting a spelling mistake in a document. If the correct version of a faulty word is re-inserted in the text at random, as with the traditional approach to gene therapy, the word is not going to make sense, and could interrupt the flow of another sentence.

RNA repair addresses this issue of context because the gene remains where it is, upregulated and downregulated as usual. 'The mutant instructions are made at the right time in development and differentiation, and in the right amounts,' said Sullenger. 'So we think we will recapitulate the right expression better by repairing them.'

Ribozymes

Sullenger uses an RNA enzyme (ribozyme), called a Group I intron, to repair RNA. These introns cleave RNA at two sites, discarding the intervening RNA, before joining the ends back together.

Crucially, if the ribozyme has a sequence attached to its tail end, it sticks this into the RNA gap before gluing the whole thing back together; replacing one piece of RNA with another. In addition, the ribozyme recognizes its cleavage sites by base-pairing, so by changing the ribozyme sequence, it can be engineered to cut at different targets.



Sullenger is looking at sickle-cell anaemia, which is caused by a defect in the gene encoding beta-globin. 'The intricacies of globin gene expression have made the development of treatments... based on gene therapy difficult,' says Sullenger, making it an ideal candidate to test out the RNA repair approach.

His team has already repaired the beta-globin RNA in red blood precursor cells from people with sickle-cell anaemia, but the process was only transient and very inefficient.

Now, the researchers have engineered the ribozyme into a viral vector to enable longer-term expression in cultured cells. They also added several structural components to the ribozyme to optimize its repair capabilities and specficity. These ribozymes are capable

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