

Newsdesk

Molecular mimicry and Gram negative infections

The frustrating lack of evidence of infection in many forms of uveitis despite the clinical suspicion and the temporal association of the uveitis with a previous attack of systemic infection is well known to clinical ophthalmologists. The clearest example is the association of acute anterior uveitis with ankylosing spondylitis and Gram negative infections. A recent paper (*Nature Medicine* 2000;6:215-18) now shows evidence of molecular mimicry in Gram negative infections. Molecular mimicry is the process whereby antigenic epitopes from pathogenic micro-organisms have sufficient similarity to self epitopes that "cross reactive" infections occur. The mechanism involves dual activation of T cells by the same peptide: one set of T cells being specific for the foreign antigen and the second set being specific for the self antigen. In fact it has been shown recently that each T cell receptor is much less selective than previously thought and has the potential to react to many more antigens. In this paper, Lo *et al* have identified an immunodominant epitope derived from the *Salmonella typhimurium* GroEL molecule. This antigen was recognised by CD8+ cytotoxic T lymphocytes induced after natural infection. In addition it was presented by the mouse H2-T23 encoded class Ib molecule Qa-1 to the same *S typhimurium* stimulated cytotoxic T lymphocytes recognising a peptide derived from mouse heat shock protein 60 (presumably) in stressed macrophages. The authors state that their results indicate a mechanism for the aetiological link between Gram negative bacterial infection and autoimmunity.

Drug discovery

The pharmaceutical industry has been heavily investing in drug discovery programmes with 50 000 pharmaceutical scientists researching more than 1000 new therapies to the tune of around £50 (\$80) billion. Both large molecules such as proteins and small molecules have been identified as targets but the latter is the preferred choice of the industry mainly because of their ease of manipulation. When the human genome has been fully sequenced (imminent) drug companies will have to set clear aims according to Fox *et al* (*Genetic Engineering News* 1999 Dec, p 10). These are to identify (a) a valid therapeutic target, (b) related molecules with which a therapeutic agent might cross react, (c) low molecular weight transporters and metabolising enzymes with which a candidate drug might interact, and (d) genetic variation in the patient population that would have an impact on therapeutic efficacy and toxicity. According to officials at Glaxo Wellcome, the merger with SmithKline Beecham will place Glaxo SmithKline in a good position to compete successfully in the new millennium by using their combined resources. This is mainly through combining expertise in several different fields such as genomics, combinatorial chemistry, bioinformatics and cell and molecular biology.

CJD and the spongiform encephalopathies

Since the explosive emergence of mad cow disease and its link with new variant Creutzfeldt-Jakob disease (nvCJD), the search

has been on to find means of treating the condition believed to be caused by the abnormal folding of the prion protein PrPsc. A team of scientists at Axonyx, Inc, (New York City) in collaboration with the Sero-pharmaceuticals Research Institute (Geneva) claims to have found that a 13-mer peptide with homology to the PrPsc can reduce the clinical symptoms in mice with prion disease as well as block infectivity of the prion molecule by more than 90-95%.

PDT

The advent of photodynamic therapy for macular degeneration has generated intense interest in development of molecules which may be specific for newly grown blood vessels. A group led by Dr Dario Neri of the National Cancer Institute (Genoa, Italy) has identified a recombinant antibody which binds to the ED-b domain of fibronectin, a region which is present only in abnormally growing blood vessels and is inserted as an alternatively spliced sequence. The antibody thus targets newly growing vessels and not mature vessels and has been shown to specifically localise to such vessels—for example, in the cornea micropacket assay. In addition, they have coupled the antibody to a red photosensitiser which allows destruction of the new vessels by appropriate laser energy while sparing the surrounding tissue. The potential for a range of ocular diseases including macular degeneration is clear.

Blindsight

Blindsight is the phenomenon whereby patients with primary damage to their primary visual cortex can still appreciate visual sensations and even images owing to what has been described as "top down" visual processing—that is, the final visual image which is eventually perceived in the intact cortex is modulated by input not only from the retina and association pathways but by primary cortical activity. It has now been shown that this process can be improved in visually impaired individuals (see review by Danckert and Goodale; *Current Biology* 2000;10:R64-7) by tapping into perceptual modes that are unaffected by the damage. For instance, use of the intact colour perception in patients with specific defects of form vision was possible by taking advantage of the fact that some colour after effects are dependent on the orientation of the stimuli used to adapt the visual system. As the authors state, after looking at a pattern of horizontal green and black lines alternating with a pattern of vertical red and black lines, people will later see an after effect of complementary colours when shown a display of black and white lines. Interestingly the colour after effects were perceived on orientations they could consciously perceive. The effects are generically described as "bootstrapping" and may represent nothing more physiological than the sparing of secondary visual pathways after damage to the primary visual cortex.

A drug to prevent retinitis pigmentosa?

The cardiac drug diltiazem appears to offer the potential for prevention of retinitis pigmentosa (RP). In an animal model of one form of RP, the rd mouse, in which the gene

for rod cGMP phosphodiesterase is mutated, Frasson *et al* report that administration of diltiazem, a calcium channel blocker, appeared to rescue the photoreceptors from degeneration (*Nature Medicine* 1999;10:1183-7). The authors suggest that in view of the extensive experience with this drug in cardiac disease it should be readily available for clinical trials in appropriate patients although the mechanism of action in RP remains unknown.

Aquaporin and CNS oedema

Aquaporins are water transporters situated in cell membranes similar to many other channel proteins. Several aquaporins have been described and regulate many cellular processes in which water transport is important. This applies to the corneal endothelium, the lens epithelium, the retinal pigment epithelium in the eye, and to glial cells in the CNS in the brain and the retina. A recent study (*Nature Medicine* 2000;6:159-63) has shown that aquaporin 4 (AQP4) regulates water transport in glial cells in the brain and that mice deficient in this membrane protein are protected from the effects of cerebral oedema induced by ischaemia or acute water intoxication. The authors suggest that AQP4 inhibition may provide a new therapeutic option for reducing brain oedema in a wide variety of cerebral disorders and it is likely that similar inhibitors may have an effect in retinal oedema especially macular oedema, the major cause of visual loss in diabetes and ocular inflammatory disease.

Award of the Crafoord Prize

Professors R Maini and Mark Feldman have been awarded the prestigious Crafoord Prize by the Swedish Academy of Sciences for "the identification of TNF blockade as an effective principle in rheumatoid arthritis". The Crafoord Prize is awarded for areas of research not covered by the Nobel Prize. Each prize winner receives a gold medal and £150 000 (\$240 000). The two researchers are based at the Kennedy Institute of Rheumatology at the University of London, supported by the Arthritis and Rheumatism Council.

Epithelial cell adhesion

The way epithelial cells from firm intercellular adhesion is central to many processes not least in the eye. For instance the barrier functions of the corneal epithelium and the retinal pigment epithelium depend on specific intercellular adhesions dependent on actin. A recent study (*Cell* 2000;100:209-19) has shown how this process is achieved. Initially there is cadherin mediated intercellular adhesion that utilises calcium to stimulate filopodia. According to the authors, the filopodia penetrate and embed into neighbouring cells in a zip-like manner and opposing cell surfaces are clamped by desmosomes, while other cytoskeletal proteins, such as vinculin and zyxin, are recruited to adhesion zippers by a mechanism that requires alpha-catenin. Actin then reorganises and polymerises to merge puncta into a single row and seal cell borders. Altogether, the results show that there is a dynamic mechanism for intercellular adhesion involving calcium activated filopodia penetration and actin reorganisation/polymerisation.



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