Abstract

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Plenary Session Papers

1. Autoimmunity to collagen type II
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Autoimmunity to cartilage-derived collagen type II (CII) can contribute to arthritis in several species of animals by means of a synergistic action between anti-CII reactive T and B cells. This presentation will address three aspects of CII autoimmunity: (i) Which factors determine whether an induced auto-reactivity to CII in rodents will result in disease or not? It appears that not only a number of genetic factors, but also the context in which CII is introduced as an immunogen is of critical importance; (ii) Which features of a disease-inducing auto-anti-CII response are of particular importance for our search for specific immunotherapy against diseases related to CII-auto-reactivity? Particular attention has to be paid to the synergy between T and B cells in collagen arthritis development; (iii) What evidence exists for a role of anti-CII reactivity in human rheumatic diseases? Evidence will be presented for the existence of a DR4-related local immune response to CII in RA and for a systemic autoimmunity to CII in SLE.

2. Autoimmunity to cartilage antigens.
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It has long been proposed that rheumatoid arthritis (RA) is an autoimmune disease. The nature of the autoantigen driving the synovitis has not been characterised. The unique tissue within the joint is undoubtedly the articular cartilage. A number of components of the articular cartilage have been proposed as possible autoantigens. This includes type II collagen and cartilage proteoglycans. The success in establishing their role as autoantigens has been variable. A novel approach has been developed in which an expression library of human chondrocytes has been constructed and this has been screened for possible autoantigens involved in the pathogenesis of rheumatoid arthritis.

3. Role of RING genes in diseases.

The human MHC spans a region of approximately 4 million base pairs on the short arm of chromosome 6 and encompasses over 75 known genes. Many human diseases are associated with the MHC, but because of linkage disequilibrium it is often impossible to assign susceptibilities to individual genes. Although associations are strongest with loci encoding class I and II MHC molecules, other linked genes may be the true susceptibility loci. Even if class I and II molecules are themselves primarily involved in disease pathogenesis, several studies have indicated that secondary susceptibility loci might be encoded within the MHC. We have isolated a number of new genes in the class II region (originally called the RING genes), some of which are attractive candidates for disease susceptibility genes. Of particular interest are the closely linked genes TAP1, TAP2, LMP2 and LMP7, which appear to play a role in class I restricted antigen processing. TAP1 and TAP2 encode two halves of an ABC transporter molecule which we believe transports peptides from the cytoplasm into the ER. LMP2 and LMP7 encode proteins with homology to components of a large intracellular proteolytic complex, the proteasome; this complex may be responsible for the degradation of protein antigens into short peptides. As a prerequisite to disease studies, we have analysed amino acid polymorphism within TAP1 and TAP2. TAP1 contains at least two polymorphic sites and TAP2 contains at least four polymorphic sites. To analyse the alleles and haplotypic combinations of the TAP genes, we used ARMS PCR to characterise the known TAP1 and TAP2 polymorphisms in a panel of 115 homozygous typing cell lines. Of four possible TAP1 alleles, we observed three, and of eight possible TAP2 alleles, we observed five. In this ethnically heterogeneous panel of HTCs, there was no indication that particular combinations of TAP1 and TAP2 have been maintained together. However, we have evidence that in some haplotypes TAP loci are in linkage disequilibrium with HLA-DR and HLA-DQ. Thus we commonly find the alleles TAP1A and TAP2A on the extended HLA-DR3-DQ2 haplotype in Caucasian controls. We are extending this analysis to MHC associated disorders such as rheumatoid arthritis, ankylosing spondylitis and coeliac disease.

4. Is there a future for peptide therapy in RA?
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Administration of synthetic peptides can induce selective immunosuppression of experimental autoimmune disease. Immunosuppression by peptides could be grouped under three major categories: 1) passive treatments aimed at inhibiting T
cell activation by blocking the MHC binding site to any antigenic peptide, including autoantigens; 2) treatments aimed at functionally incapacitating the autoreactive T cells, either by administration of autoantigenic peptides in tolerogenic form, or by TCR antagonists able to induce selective T cell anergy; and 3) vaccination-like treatments aimed at inducing or enhancing regulatory T cells able to control the activity of pathogenic, autoreactive T cell. The efficacy of these T cell immunosuppressive strategies has been verified in several experimental autoimmune models, including models for RA. Conversely, development of these approaches for clinical testing in RA is just beginning, mainly because information on the autoantigens involved is still fragmentary and not fully verified. Hopefully, the active research in this area may soon permit the identification of reliable autoantigen candidates. Weak points of peptide-based immunotherapy of human autoimmune diseases are the requirement for parenteral administration and the relatively short plasma half-life of synthetic peptides. It is however possible to modify these unfavorable characteristics of synthetic peptides by constructing peptide-mimetic drugs, and by utilizing appropriate delivery systems. If RA is a T cell-dependent autoimmune disease and if the autoantigens are of limited heterogeneity there is a future, albeit perhaps not near, for peptide therapy in RA.

5. Modelling arthritis in transgenic mice.

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Gene addition and gene deletion in transgenic animals can be used to address questions of gene function and to evaluate the involvement of deregulated gene expression in the development of inherited or acquired human disease. We have recently reported (EMBO J. 1991; 10:4025) that transgenic mice expressing a 3'-modified human tumour necrosis factor (TNF) transgene, develop chronic inflammatory polyarthritis with 100% phenotypic penetrance. Inflammatory infiltrates of the synovial space, fibrous tissue and pannus formation, articular cartilage destruction and bone resorption are observed, all typical histological characteristics of human rheumatoid arthritis. Development of arthritis in these transgenic mice can be completely suppressed by treatment with antibodies against huTNF, confirming that the pathology observed is effected by the in vivo deregulated production of huTNF protein. We are currently investigating the character of the perturbance that triggers the development of arthritis in these TNF transgenic mice. Using in situ hybridization and immunocytochemical analysis of transgenic joint tissue, we can show that as in human rheumatoid arthritis, tumour necrosis factor is produced by synovial lining cells and at the cartilage/pannus junction. We are considering that TNF action may be either direct, for example by driving proliferation of synoviocytes and contributing to local inflammation in the joint, or indirect, possibly by interfering with immune homeostasis in the joint space. Experiments are under way to test these possibilities and to further characterize this transgenic mouse model of human arthritis.

Several different factors such as immunogenetic susceptibility, infectious agents and endogenous substances have been implicated in triggering the primary immune response in arthritis. Later in the development of the disease, immune and non-immune effector mechanisms mediated by the action of cytokines, adhesion molecules, growth factors, neuropeptides and other inflammatory mediators have been considered important components of the pathogenetic process. The functional hierarchies operating amongst this network of factors and their differential contribution in the development of disease can potentially be exploited by perturbation analysis in transgenic systems.

6. TNFα as a therapeutic target in rheumatoid arthritis.


Analysis of cytokine expression in the rheumatoid synovium revealed that many cytokines were produced locally. In order to evaluate which of these were of major importance, we initially focussed on the regulation of the cytokines involved in joint destruction, IL-1 and TNFα, and found that neutralising antibody to TNFα also abrogated IL-1 production. Thus TNFα seemed a promising therapeutic target, and subsequent studies in vivo in the collagen arthritis mouse has validated this concept, as joint inflammation and particularly destruction was ameliorated. Based on this data, and the availability of a potent neutralizing human IgGl/mouse Fv chimeric antibody to TNFα, cA2, an open Phase VII clinical trial to evaluate the effect of neutralising TNFα in RA patients which had already failed multiple disease modifying drugs was initiated. In all 10 patients there was a profound fall in CRP and reduction in ESR. There was rapid and marked clinical response in all patients, as judged by > 70% improvements in pain scores, early morning stiffness, Ritchie Index and swollen joint count. This data supports our hypothesis that TNFα plays a central role in the pathogenesis of RA, and indicates that TNFα is a useful therapeutic target in this disease.

7. Cytokine gene polymorphisms.

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We have characterised by gene sequencing 5 novel polymorphisms in the non-structural regions of human cytokine genes. These include the pro-inflammatory TNF alpha, IL 1 beta, IL 1 alpha genes and the anti-inflammatory IL1 receptor antagonist. The polymorphisms are either bi-allelic (single base substitution 5' of first exon) or multi-allelic (variable number of intronic repeats). They have been confirmed by pedigree analyses and allelic frequencies were determined in several normal populations in the UK and Europe. In collaboration with centres in the UK, Holland, Norway, Germany, Denmark and Switzerland we have found that the TNF alpha uncommon allele on chromosome 6 is strongly associated with the “autoimmune MHC haplotype” A1, B8, DR3 (RR = 79). It also appears to be associated in individuals with high production of TNF alpha. The mechanism of this and the functional significance of the chromosome 2 polymorphisms is currently being assessed. Each one of these polymorphic cytokine genes have alleles that are significantly associated with