Recent advances in autoimmune diseases

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This conference, held at the Royal College of Physicians on 11 May 1999, was organised by Professor Margaret Bassendine, Professor of Hepatology, University of Newcastle.

Autoimmune diseases affect up to 5% of the Western population[1]. Study of autoimmune disease in humans – an 'experiment of nature' where the normal mechanisms of immune self-tolerance break down – has also provided important information regarding the ways in which the normal state of tolerance to self is maintained. Recent advances in our understanding of the pathogenesis and therapy of human autoimmunity were the topic of this conference.

Pathophysiology of autoimmune disease

The immune system of mammals represents the culmination of millions of years of evolutionary pressure. Until (very) recent times this pressure has arisen almost exclusively from the effects of infectious disease on the evolutionarily relevant young adult population. Effector mechanisms able to clear invading parasites from the host are the *sine qua non* of a functional immune system. Study of human disease provides powerful examples, however, of the damaging effects of continual or inappropriate activation of these effector systems. Survival advantage is therefore only likely to be conferred on the host if the application of immune effector mechanisms is selective, and appropriate to the context in which any immune stimulus is encountered.

Selectivity and the immune response

Many cells of the evolutionarily more primitive innate system, such as macrophages and neutrophils, undergo activation in response to chemical or 'pattern recognition' factors unique to infectious organisms, resulting in some selectivity in their response. However, the diversity of these selectivity factors for the innate immune response is limited. Moreover, as infectious organisms are themselves subject to evolutionary pressure (and 'reproduce' at a dramatically higher rate than their hosts), pathways evolved to escape these limited selectivity factors.

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As a result of this evolutionary pressure, the more highly developed immune system in mammals has evolved the specific immune response – a second tier of selectivity with an almost infinite capacity to develop responses to foreign protein antigens through the mechanisms generating diversity in the T-cell receptor and immunoglobulin genes. This infinite capacity to respond to proteins can be an extremely effective tool for the protection of the host: regardless of the extent to which infectious organisms can change their protein identity, the immune system is likely to have a responding cell with randomly generated response specificity. However, through generation of responses wholly reactive with self-antigens, it can also cause damage to the host.

The specific immune system has therefore evolved a series of 'checks and balances' to discriminate harmless self (self-antigen seen in a non-inflammatory environment) from harmful non-self (foreign antigen encountered in the context of an inflammatory environment) whilst permitting the existence of harmless non-self (for example a dietary antigen encountered in the absence of inflammation)[2]. Autoimmune disease results when this discriminant function fails.

Conference programme

- **Genetic susceptibility to autoimmunity**
  Professor J A Todd, Cambridge Institute for Medical Research
- **Viruses and autoimmunity**
  Dr P J W Venables, The Kennedy Institute of Rheumatology, London
- **Mechanisms of tolerance to self**
  Professor A Basten, Centenary Institute of Cancer Medicine and Cell Biology, Newtown, Australia
- **Complement disorders in autoimmunity**
  Professor M J Walport, ICSM, Hammersmith Hospital, London
- **Cytokines and autoimmune thyroid disease**
  Professor A P Weetman, University of Sheffield
- **Autoimmune hepatitis**
  Professor A L W F Eddleston, Guy's, King's and St Thomas' School of Medicine, London
- **Anti-cytokine therapy for rheumatoid arthritis**
  Professor D Isenberg, Centre for Rheumatology, University College London Hospitals
- **The basis for treatment in multiple sclerosis**
  Professor D A S Compston, University of Cambridge
- **Clinical trials in vasculitis**
  Dr D Jayne, St Helier Hospital, Carshalton and St George's Hospital Medical School, London
- **Towards antigen-specific therapy**
  Professor D C Wraith, University of Bristol

Genetic factors and environmental triggers

The conventional and widely held view is that autoimmunity occurs when a genetically susceptible individual encounters a 'trigger' capable of disturbing the normal state of immune self-tolerance. The evidence in favour of this model comes largely from studies of disease patterns within families. Autoimmune diseases have been widely reported to be concentrated within families, suggesting a role for genetic factors in determining disease susceptibility. Data from interval mapping (whole genome scanning), and case control gene association studies, have primarily implicated the major histocompatibility complex (MHC) in susceptibility to autoimmunity. Interest has also recently focused on other loci (for example the T-cell surface marker CTLA-4) which show strong disease associations and which encode proteins playing additional fundamental roles in the control of induction and termination of T-cell responses. A further locus identified as a susceptibility marker in type I diabetes is a promoter polymorphism in the insulin gene. It has been proposed that the protective allele at this locus increases low level expression of insulin in the thymus allowing continual deletion of potential insulin-derived epitope-specific T-cell-precursors during thymic ontogeny.

Data derived from autoimmune disease families, in particular the lack of complete penetrance of diseases such as type I diabetes in monozygotic twins, have also emphasised the role played by additional factors in disease induction, which are presumed to be environmental in nature. The ability of infectious organisms to shape the normal immune system has led to the suggestion that these environmental triggers for autoimmunity are infectious agents. However, the data directly implicating specific infectious agents in individual diseases are limited, and the whole concept of simple infectious triggers for autoimmunity in genetically 'primed' hosts has recently been challenged. Emerging data from human populations suggest that multiple infections in the first few years of life may protect against the subsequent development of one autoimmune disease (type I diabetes). Equally challenging is the observation that the prevalence of diseases such as type I diabetes has increased markedly over the last 30 years, a time when improvements in hygiene and control of childhood infections through programmes of vaccination may have significantly reduced the burden of infection in the early years of life.

Viruses

In Sjögren's syndrome, attention has focused on the Herpes viruses and retroviruses, with emphasis on sialotrophic and lymphotrophic agents with the capacity for latent or persistent infection. Epstein-Barr virus (EBV), which encodes a large number of immunomodulatory proteins and which is B-lymphotropic and epitheliotropic, is one such candidate trigger. Four case reports have linked EBV infection with the subsequent development of Sjögren's syndrome, whilst antibodies to a number of EBV proteins have also been reported (variably) in Sjögren's syndrome.

Retroviruses are present in two forms in humans: the infectious retroviruses and the endogenous retroviruses (which result from the incorporation of a proviral genome into the human genome and which are inherited in a Mendelian fashion). The caprine arthritis encephalitis virus (a ubiquitous retrovirus in goats affecting up to 90% of animals in some herds) can induce an MHC linked polyarthritis in a minority of infected animals. In humans, a range of rheumatic syndromes has been described in HIV infection. Low levels of antibody against retroviral Gag proteins have been described in both Sjögren's syndrome and lupus. Attempts have been made to isolate putative infectious retroviruses by co-culturing affected labial biopsies with susceptible cell lines and screening for viral derived proteins and nucleic acids. These approaches have shown promise for the isolation of retroviruses inducing autoimmunity in humans.

The complement system in autoimmunity

Systemic lupus erythematosus (SLE) is characterised by specific autoantibody responses to intracellular antigens (in particular nuclear and related antigens including chromatin, the spliceosome and the Ro & La small cytoplasmic ribonucleoprotein particles [scRNP]). Other autoantibodies include those directed at phospholipids normally found on the inside of the cell membrane. The link between these antibodies and the mechanism of tissue damage has remained an area of much speculation, although immunohistochemical studies of affected tissues (such as the glomeruli) suggest deposition of both antibodies and immune complexes together with complement derived proteins. Studies of the rare patients with inherited complement abnormalities (such as the 41 reported patients with homozygous C1q deficiency, the majority of whom developed SLE or discoid lupus early in life) suggest that there is a hierarchy of susceptibility to lupus related to the position in the complement cascade of the component encoded by the mutant gene, with C1q deficiency at the top. These observations suggest a role for the early factors in the classical complement cascade in protection against SLE. One such potential role is to clear immune complexes. To address the question of the role played by activation of the classical complement pathway in SLE, a targeted mutation mouse model of C1q deficiency has been developed. Between six and eight months of age 25% of the C1q -/- 'knockout' mice die of glomerulonephritis, with histological and immuno-histochemical features similar to those seen in SLE patients.

Data increasingly suggest a role for apoptotic cells (expressing SLE related autoantigens aberrantly on their surface) in the generation of autoantibodies driving immune complex formation in SLE. As C1q can bind to apoptotic keratinocytes, this suggests a possible role for the classical component cascade in the clearance of apoptotic

cells, and a possible mechanism whereby C1q deficient animals could be susceptible to immune-complex driven glomerulonephritis. Strikingly, C1q deficient animals demonstrate increased frequency of apoptotic cells in their glomeruli, and decreased clearance of apoptotic cells in an *in vitro* model – findings which appear to support this model.

Cytokines

Thyroid disease has served as a model for the role played by cytokines in autoimmunity. The mutually regulating Th1 and Th2 phenotype T-cell responses are characterised by cytokine patterns that produce contrasting effector mechanisms (Th1 phenotype cells secrete interferon [IFN]-γ and support cellular responses [for example in Hashimoto's thyroiditis], Th2 phenotype cells secret interleukin [IL]-4 and IL-5 and support mature humoral responses [for example in Graves' disease]). Although of value, this paradigm represents an over-simplification of the complex inter-relationships of different functional cell sets[3].

Cytokines also exert direct effects in autoimmunity. Thyroid-associated ophthalmopathy results from cytokine induced swelling of the extra-ocular muscles by an inflammatory infiltrate consisting primarily of activated T-cells. The muscle fibres are intact but show increased spacing as a result of glycosaminoglycan production by fibroblasts in the muscle. These fibroblasts are stimulated by local cytokines secreted by autoreactive T-cells. The response of the orbital fibroblasts is a particular characteristic of cells from this site, and is marked in comparison with equivalent cells from other tissues such as the dermis. This apparent difference in function may go some way to explain the tissue tropism of fibroblast mediated pathology seen in thyroid associated ophthalmopathy. Interrupting this pathway may represent a potential approach to treatment of this clinically important manifestation of autoimmune thyroid disease.

Therapy of autoimmune disease

Rheumatoid arthritis

As disruption of regulatory cytokine networks undoubtedly contributes to the pathophysiology of autoimmune disease, therapy aimed at restoring the normal regulatory balance is an attractive concept.

Anti-cytokine therapy for rheumatoid arthritis (RA) aims to block tumour necrosis factor (TNF)-α function using either humanised murine monoclonal antibodies to TNF-α or soluble TNF-α receptor molecules. A single dose of the agent CA2 (infliximab) suppresses synovitis and serum inflammation markers for up to 6 weeks (in up to 80% of treated patients using optimal doses), whilst multiple treatment regimes showed effects on severity of joint involvement. Similarly, up to 80% of patients treated with chimeric molecules consisting of recombinant TNF-α receptor and IgG constant region show a clinical response. Combination of anti-TNF-α antibody with conventional treatments such as methotrexate has a useful anti-TNF-α dose sparing effect. Other approaches to cytokine based therapy in RA have included blocking IL-1, IL-6 and IL-10 although, to date, these remain purely experimental.

Multiple sclerosis

Damage in the brain in multiple sclerosis (MS) is conventionally thought to follow an orderly cycle of inflammation (presumed to have an autoimmune element), tissue damage and then fibrosis, leaving tissue with naked but intact axons which conduct nerve impulses only poorly. This is probably an oversimplification. In particular, axon damage may occur relatively early in the disease process. The apparently critical part played by inflammation in the pathogenesis of MS suggests a role for anti-inflammatory agents in therapy, exemplified by the use of interferon beta, an anti-inflammatory agent which reduces microglial cell class II expression. Interferon beta has been shown, in four trials, to reduce clinical relapse rate by one third. There is a more marked effect on surrogate markers of disease severity such as numbers of gadolinium enhancing brain lesions on magnetic resonance imaging (MRI) scanning. The relevance of this effect on hard clinical markers is, however, less clear. A trial of the effect of interferon beta on the progressive phase of the disease suggests a modest beneficial effect.

Our increasing appreciation that the inflammatory response plays a critical role in both the (helpful) repair as well as the (harmful) effector phase of the auto-immune process in MS means that approaches targeted more specifically at the autoreactive T-cell response (exclusively harmful) using the humanised mouse monoclonal antibody anti-CD52, a profoundly effective T-cell depleting antibody (whose effects can last for years following a week of treatment), may be clinically more productive. Anti-CD52 treatment reduces new brain lesion development (as assessed by gadolinium enhancing lesions) and the development of new clinical manifestations over 18 months following therapy. Intriguingly, thyrotoxicity developed in a number of patients treated with anti-CD52 in the second year after treatment. This was the only significant apparent side-effect of the treatment. In contrast to the beneficial effects on the induction of new lesions, progression of existing lesions occurred in up to 50% of patients treated with anti-CD52. Progression was associated, both before and during treatment, with the presence of brain atrophy resulting from axonal loss. The contrasting outcomes in treatment suggest clearly that events related to the induction of new lesions must be separated from the consequences of progression of existing damage. The conclusion of trials which demonstrate efficacy in modulating the former but not the latter is that agents such as anti-CD52 should be used early in the disease process, before the development of a significant element of chronic oligodendrocyte loss likely to result in progression of damage which is unresponsive to treatment.

The importance of the design of future clinical trials of new therapies aimed at modulating fundamental immunological processes is therefore clear.

Clinical trials and autoimmunity

The results achieved in these evolutionary trials emphasise the importance of logical series of trials which build on the results (beneficial or otherwise) of earlier trials. Although the lure of new 'miracle' treatments for a particular disease is great, it is often the case that learning to use the drugs that are already available in an optimal fashion (through the identification of appropriate patients, selection of the correct dosing regimes, the use of logical drug combinations and identifying the correct outcome measures for use in a trial) provides greater patient benefit (at least in the short term).

Antigen specific therapy

If antigen specific immune responses, orchestrated by CD4+ 'helper' T-cell responses, are responsible for tissue damage in autoimmune disease then perhaps, theoretically, the most attractive approach to treatment is to target only those cells and immune effectors which are specific for the relevant autoantigen. This potentially has the advantage of leaving the residual immune system intact, thereby, in theory at least, reducing the adverse effects of therapy. The vast majority of data available to date derive from animal models, and in particular experimental autoimmune encephalomyelitis (EAE). Nasal administration of epitope peptides derived from myelin basic protein (the dominant autoantigen in EAE) can prevent the development of the disease. Oral administration of antigen is less effective (an issue of importance for the design of future human studies). Of particular relevance for the use of antigen-specific therapies in human disease is the observation that administration of peptide by the nasal route after the induction of disease has an appreciable disease ameliorating effect, although it is clear that application at the earliest possible point in the disease course is likely to generate the greatest clinical effect.

Conclusion

We can draw three conclusions from this provocative meeting. The first is that our understanding of the mechanisms which lead to a failure of immune self-tolerance and result in autoimmunity is increasing rapidly. The second is that this increased understanding will generate many exciting theoretical and experimental approaches to therapy. The third is that the next stage in the process, the development and assessment of such treatments for use in human populations, may be the most difficult of all.

References

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