

RHEUMATIC DISEASES

*Immunological mechanisms and prospects
for new therapies*

Edited by

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1

Implications of advances in immunology for understanding the pathogenesis and treatment of rheumatic disease

J. S. H. GASTON

Advances in immunology

This book has been designed to meet the needs of those whose clinical or research interests are in rheumatic diseases. Within rheumatology, there has been a lively debate on the relevance or otherwise of advances in immunology to a better understanding of rheumatic diseases and their treatment. Until relatively recently, it would have to be conceded that treatment of a disease like rheumatoid arthritis (RA) has been based on empirical observation of the usefulness of certain drugs (usually tested originally on the basis of some wholly erroneous idea about pathogenesis); in short, rational therapies based on a new understanding of immunopathology were in short supply. This situation is now changing, with the successful application of 'biologic' treatments, such as antibodies to tumour necrosis factor alpha (TNF α), or recombinant interleukin 1 (IL-1) receptor antagonist in RA (Arend & Dayer, 1995; Maini *et al.*, 1995), and the initial exploration of supplying such therapy by means of gene transfer (Evans & Robbins, 1996). It is very likely that much of the therapeutic effort of rheumatologists in the first part of the 21st century will be directed to defining the place of novel biological therapies in the management of rheumatological disease, while determining in more detail the mode of action of current empirical therapies so that they may be used to best advantage.

In order to participate in this process, it is necessary to have at least some working knowledge of the components of the immune system, and how they might be implicated in rheumatic disease. Although there may have been some dissatisfaction with the relatively small contribution of immunologists to the therapy of rheumatic disease since the late 1960s, it was clearly unrealistic to expect a major therapeutic impact on disease at a time when so little normal immune physiology had been defined. There has been an enormous explosion in knowledge since the late 1970s, and this process continues, fuelled by the power

of current molecular techniques. In 1982, three interleukins had been characterized, whereas the number is now approaching 20. To these can be added those cytokines that for some reason do not qualify for interleukin status, such as TNF (three varieties), oncostatin-M, leukaemia inhibitory factor (LIF), and many others, most having names that completely fail to indicate the wide range of their involvement in inflammation and immunity – none of the three examples quoted has effects confined to neoplasia.

To these must be added a plethora of chemokines; around 40 are defined, but there are perhaps as many as 60 additional expressed-sequence tags (ESTs) that have features which make them putative chemokines (Schall & Bacon, 1994). The set of chemokines join IL-8, otherwise a somewhat anomalous member of the interleukin family. There are four major families of chemokines (CKs), classified according to the number and position of cysteine residues at their amino terminus. These are termed the C-X-C, C-C and C families (Baggiolini, Dewald & Moser, 1997), along with the recently described C-X₃-C chemokine (Bazan *et al.*, 1997). The predominant actions of chemokines are on neutrophils (C-X-C family) or monocytes and lymphocytes (C-C, C and C-X₃-C families). An expanding family of receptors (CCRs and CXCRs) for these factors is also being defined. Faced with so many factors and receptors' it is tempting to assume substantial redundancy, and this is certainly the case for some functions (e.g. neutrophil chemotaxis), but recent investigations in HIV infection clearly show that polymorphisms in single chemokine receptors can have measurable effects on clinical outcome (Garred, 1998). For HIV, these effects probably reflect the fact that the virus hijacks the chemokine receptor to gain access to cells. Nevertheless, it is possible that associations between polymorphisms, in particular chemokine or chemokine receptor genes, will also be discovered with respect to rheumatic diseases when the genetic influences on disease incidence and characteristics are unravelled by current whole genome search strategies.

The most recent chemokines and chemokine receptors to be described are examples of 'reverse genetics', with the first inkling of their existence coming from DNA sequences rather than a biological activity (Forster *et al.*, 1996; Bazan *et al.*, 1997; Gunn *et al.*, 1998a,b). This effectively short-circuits the previous labour-intensive procedure of purifying, sequencing, cloning and expressing new biologically active factors. A similar route has also been used to define new cytokines such as IL-17 (Yao *et al.*, 1995a,b). Amongst newer chemokines are factors that have important roles in establishing the architecture of the immune system, by, for instance, attracting cells into germinal centres (Gunn *et al.*, 1998a). Since the rheumatoid arthritis synovium can take on the architectural appearance of a lymph node, including germinal centre formation, this is likely to reflect

chemokine production within the tissue, and the particular stimuli that give rise to this response in chronic inflammation will be of great interest.

Cell surface molecules on lymphoid and myeloid cells are now defined to the extent of more than 160 CD (cluster of differentiation) numbers, where 15 were required in 1982 (Shaw, Turni & Katz, 1998) (<http://www.ncbi.nlm.nih.gov/prow/>). Some of these can be cleaved from cell surfaces and then act as cytokines or can modulate cytokine action by binding them in solution. The precise function of many of these surface molecules has yet to be defined, but even at our current partial stage of understanding, the cells that make up the immune system are amongst the most thoroughly characterized in the whole body. It is evident that things have changed substantially from the classic description of the lymphocyte as a 'small round cell . . . of which literally nothing of importance is known' (Gowans, 1996).

At one time, the interests of cellular immunologists were almost entirely focused on events at the cell surface, the cell itself being treated as something of a 'black box', but now many signalling pathways have been defined in great detail and shown to be very complex. Examples include signalling from T and B cell receptors, from co-stimulatory molecules and cytokine receptors, and the signalling mechanisms that mediate programmed cell death (apoptosis). Many of the components of the signalling pathways are not used uniquely by the immune system, and signalling pathways used by hormones and growth factors commonly intersect with those of lymphocytes. In addition, many of the transcription factors that are important in lymphocyte activation have a wide spectrum of activity in the activation of other genes (an example would be NF κ B). However, signalling components and transcription factors that have a very particular role in the immune system have also been discovered; signalling through the IL-12 receptor is wholly dependent on the signal transducer and activator of transcription STAT-4 (Thierfelder *et al.*, 1996), whereas STAT-6 is required for the actions of IL-4 (Shimoda *et al.*, 1996; Takeda *et al.*, 1996). Deficiency in a single tyrosine kinase, Btk, accounts for Bruton's X-linked agammaglobulinaemia (Vetrie *et al.*, 1993). Increasing knowledge of signalling pathways is likely to be particularly important since it is often more realistic to manipulate the immune system by interfering with signalling pathways using conventional pharmacologic approaches, rather than using biological agents that act primarily on cellular interactions. Even where components of a signalling pathway are used for several biological functions, it is sometimes possible to obtain a useful therapeutic effect on one of the functions without necessarily producing the same phenotype as a genetic knock-out. A recent paper suggested that sulphasalazine, widely used in rheumatology with good efficacy and safety, has its effects by inhibiting the transcription factor NF κ B (Wahl *et al.*, 1998), even though NF κ B has multiple

actions and genetic knock-out of certain NF κ B components can be highly deleterious (Baldwin, 1996).

These are just some examples of the exponential growth in knowledge of the immune system; equal attention could be paid to work on the multiple components of the major histocompatibility complex (MHC), the formation and structure of antigen-specific receptors, the components involved in the induction of apoptosis and its role in control of immune responses, and the mechanisms underlying lymphocyte homing and recirculation – to mention only a few areas that have undergone intense scrutiny and are highly likely to be relevant to the pathogenesis of rheumatic diseases.

Faced with the baroque complexity of the immune system, which now genuinely rivals the central nervous system as a finely tuned physiological mechanism, the rheumatologist who has not previously had to grapple with immunology might be tempted to despair. This book is designed to dispel such feelings. Although it would be foolhardy to imply that our current knowledge of immunology is other than partial, a large proportion of the immunological events that are likely to be responsible for rheumatic diseases have already been defined. This is not to say that we know the immunological basis of most rheumatic diseases – from it; rather we have a reasonably comprehensive list of the kinds of thing that might go wrong and can now determine those which actually do cause disease. To take a non-rheumatological example; prior to the discovery of the CD40–CD40-ligand interaction (Disanto *et al.*, 1993), the mechanism of the sex-linked hyperIgM immunodeficiency (HIgM) syndrome was completely unknown. Although it is clearly possible, and indeed likely, that additional co-stimulatory molecules remain to be discovered, deficiencies in these will have some phenotypic similarities with the lack of CD40-ligand (CD40L), which is responsible for HIgM syndrome. Likewise, prior to the description of the cytokine IL-12, certain patients who had difficulty in combating infection by intracellular organisms such as salmonellae and atypical mycobacteria had an immunodeficiency that was unexplained. Recently, patients with just this clinical phenotype have been discovered to have abnormalities in IL-12 (Altare *et al.*, 1998a) or its receptor (Altare *et al.*, 1998b). In keeping with the physiological role of IL-12 in influencing interferon- γ (IFN- γ) production, a somewhat similar phenotype has been seen in patients with defective IFN- γ receptors (Jouanguy *et al.*, 1996). Thus, gradually, clinical phenotypes are being matched with abnormalities in defined components of the immune system. Although this is most easily done where there is the equivalent of a genetic knock-out in humans, more subtle defects that might contribute to the pathogenesis of rheumatic diseases are currently being sought.

Overview of this volume

The objective in each of the remaining chapters of this review is to describe current knowledge of the principal immunological mechanisms in order to provide a physiological 'map', which can then be used to indicate components that might 'go wrong' in rheumatic disease, or components that might in the future be useful targets of therapy. Examples of known defects, and therapies that have been found effective, are provided, but the up-to-date description of the immune system should provide a framework that will facilitate future thinking about the pathogenesis of rheumatological disorders, and an understanding of the rationale behind the novel therapies currently being dreamt up by biotechnology companies.

Specific immune responses begin with antigen recognition and the receptors that mediate this: surface immunoglobulin in the case of B cells, and the different forms of the T cell receptor for antigen. Autoantibodies, which are associated with rheumatic diseases and, in some cases, are directly pathogenic, have now been studied in great detail using molecular techniques, particularly from a structural point of view. The mechanisms whereby specific antibodies are generated, and the properties of particular autoantibodies, are described in Chapter 4.

T cell receptors differ radically from immunoglobulins in their inability to distinguish intact antigen; instead they recognize short peptides that result from processing and which are then presented by means of molecules encoded in the MHC (known as the human leukocyte antigen (HLA) system in humans). This difference has profound implications for our understanding of autoimmune T cell responses, and how these might arise. The concept of 'molecular mimicry' has been put forward for some time in relation to autoimmunity (Oldstone, 1990). Mimicry occurs when antigenic determinants on pathogens (e.g. viruses or bacteria) resemble a determinant on a self-protein, so that an immune response to one cross-reacts with the other. Recently, a first example of this postulated mechanism has been documented in the keratitis induced by infection with herpes simplex virus type 1 (Zhao *et al.*, 1998). Initially, molecular mimicry was considered in relation to cross-reacting antibodies, where, for linear determinants that reflect a particular amino acid sequence, it is possible simply to compare the sequence of an autoantigen with that of a candidate mimic (e.g. a viral protein) to look for regions of sequence conservation. However, for a peptide to be recognized by a T cell there are only two requirements: it must bind to MHC and have appropriate amino acids to contact the T cell receptor. This means that there may be little or no linear sequence conservation between potential mimics, and they have to be sought in other ways. The necessary approaches are described in Chapter 2, having been pioneered by Wucherpfennig and Strominger (1995).

The prominent associations between MHC alleles and various rheumatic

disorders represent the most compelling evidence for the involvement of T lymphocytes in pathogenesis: the B27 – ankylosing spondylitis association is still, after 25 years, the strongest for any disease (Brewerton *et al.*, 1973). Despite the strength of these associations for both spondyloarthropathies and RA, and the intense scrutiny of HLA since the associations were first described, the mechanisms underlying them are frustratingly obscure and may well be different for different diseases. Hoyt Buckner and Nepom describe current understanding of the components of the MHC, how they function in immune responses and likely ways in which diseases might be associated with particular alleles (Chapter 3).

The idea that recognition of antigen alone would not be a sufficient signal for activation of B or T cells was predicted early on (Bretscher & Cohn, 1970) and has proved to be the case. Two chapters in this volume (Chapters 5 and 6) deal with important co-stimulatory receptor ligand pairs that have been identified in recent years and that are involved in T cell stimulation. The first of these involves, on the T cell, CD28 and the related molecule CTLA-4, both of which can bind to two other related ligands on antigen-presenting cells, B7.1 and B7.2. The second is CD40L on T cells, which binds to CD40 on antigen-presenting cells, particularly B cells. The importance of these interactions is underlined by the ability to induce allograft acceptance by blocking both pathways – a measure of the severe degree of immunosuppression that is produced (Larsen *et al.*, 1996). However, although CD28 and CD40 were first described as important molecules for T cell and B cell co-stimulation, respectively (prior to the discovery of their ligands), the situation is inevitably more complex. Not only can T cells express B7.1/7.2 and CD40, and B cells CD40L, but in all cases the interaction of these receptor – ligand pairs results in a two-way conversation. Thus, there are important effects on both T and B cells in the CD40L–CD40 interaction, and the same ligand pair is involved in interactions between T cells and antigen-presenting cells, particularly dendritic cells. The same is true for CD28–B7.1, with additional complexity resulting from the inducible expression of CTLA-4 as an alternative ligand for B7.1/7.2 (Thompson & Allison, 1997). The interactions have implications for antibody production, the cytokine programme carried out by activated T cells, and immunity to intracellular pathogens; both co-stimulatory pathways are already being targeted in immunomodulation strategies (Durie *et al.*, 1993; Webb, Walmsley & Feldmann, 1996).

Appropriate engagement of B and T cell receptors by antigen has profound consequences for the cell, such as entering the cell cycle, expressing activation markers on its surface and producing cytokines; in effect, an entirely new genetic programme is initiated and there are multiple differences in gene transcription (involving hundreds of genes) between activated and quiescent T or B cells. To achieve this, intracellular signalling mechanisms are required; in the first instance,

both B and T cells are dependent on components of the receptor complex other than those necessary for antigen recognition to initiate cell signalling. Other surface molecules, including the co-stimulatory molecules alluded to in the previous paragraph, can ‘fine-tune’ the response, again acting through their influence on components of the signalling pathway. Current understanding of these processes, and prospects for modulating intracellular signalling with drugs, are detailed in Chapter 7. It is clear that the notion that encounter with antigen would translate a T or B cell from an ‘off’ to an ‘on’ state in some all-or-nothing manner is quite inadequate. The effects of antigen on an antigen-specific cell will reflect the balance of positive and negative signals, in much the same way that a smooth motor action by a limb represents the graded activation of agonist and antagonist muscles rather than unopposed agonists. Indeed, there is an increasing need for such a balance in the interplay of antagonists and agonists in fine accurate movements. In addition to the signalling components involved in this process, the influence of the proportion of receptors on a cell that are activated, and the time for which they are activated, have recently been shown to be critical for the final outcome (Valitutti *et al.*, 1995; Viola & Lanzavecchia, 1996; Iezzi, Karjalainen & Lanzavecchia, 1998).

None of the mechanisms for antigen recognition and the signalling of appropriate responses addresses the question of the geography of the immune system; immune responses take place at certain sites, both within the lymphoid system and in the tissues generally, and ways of ensuring that effector cells are delivered to appropriate locations are an essential component of the immune system. This has been a very active field of research, and an overview is provided by Pitzalis (Chapter 8). Lymphocyte trafficking to appropriate tissue requires expression of ligand on endothelial cells that can be recognized by leukocytes; in fact multiple ligands are involved in the arrest and eventual transmigration of cells across the endothelium into the tissues. More recently recognized components in the process are the chemokines produced by endothelial cells and recognized by specific receptors on the leukocytes (Gunn *et al.*, 1998b); the chemokine–receptor interaction, in turn, modulates the affinity of the integrins required for firm adhesion of cells to the vessel wall. Again there are hopes that it may be possible to modulate leukocyte traffic therapeutically, and attempts to do this have already been made (Kavanaugh *et al.*, 1994).

Having dealt with the principal mechanisms for recognizing and making appropriate responses to antigens, it is important to examine the downstream effects of the antigen-specific responses, since these are the processes that turn immunological recognition into disease. In relation to inflammatory arthritis, it is clear that the synovium is dominated by the presence of macrophage/monocyte-derived rather than T cell-derived cytokines, although the recent description of a novel

cytokine, IL-17, exclusively produced by T cells but with monokine-like effects may alter this perception (Spriggs, 1997). However, there is good evidence that the monokines are directly responsible for joint destruction. Much attention has focused on the two principal monokines: TNF α and IL-1. The relative importance of each and therapeutic possibilities of inhibiting either or both are discussed by van den Berg and van de Loo (Chapter 10). This review also emphasizes the possible roles of the more recently described proinflammatory monokines such as IL-12 and IL-15, and the production of regulatory monokines such as IL-10 and transforming growth factor beta (TGF β). It is clear that the effects of blocking one cytokine or adding another are not readily predictable in relation to arthritis, with differing effects depending on the clinical endpoint examined (e.g. joint swelling versus cartilage destruction), and depending on the phase in the evolution of arthritis at which they are applied.

Immune responses have to be controlled at the level of initiation by fine tuning their magnitude and ensuring that their consequences (production of a cytokine or immunoglobulin subclass) are appropriate to the context, e.g. IFN- γ to deal with mycobacterial infection, IgE production for an intestinal helminth. However, it is equally important to have mechanisms for ensuring that appropriate immune responses do not continue indefinitely, and the principal mechanism used by the immune system at all levels involves apoptosis. Apoptosis as a mechanism for the removal of immune or inflammatory effectors after they have performed their required actions is now realised to be of critical importance for normal immunological health. Strains of mice, which were already under scrutiny as examples of spontaneous systemic lupus erythematosus (SLE)-like illness, proved to lack molecules important in one of the major pathways for inducing apoptosis, Fas (in MRL *lpr/lpr* mice) or its ligand (FasL) (in C3H *gld/gld* mice). The mechanisms of apoptosis, the molecules involved (which have rapidly proliferated in recent years) and the regulation of the process are discussed in Chapter 9.

A further level of control in the immune system concerns the recognition of self-antigens. At one time, it was simply assumed that this was forbidden, and indeed mechanisms that allow the deletion of effector T and B cells with high-affinity receptors with self have been worked out in great detail (Kappler, Roehm & Marrack, 1987). However, it has also become apparent that potentially autoimmune effector cells are part of the normal B and T cell repertoire and that, in fact, the functional immune repertoire is selected on the basis of an ability to recognize self MHC-peptide complexes (Blackman *et al.*, 1986). In any case, a repertoire that deleted every cell that could recognize an epitope present on some self molecule would be fatally compromised, since there is considerable (possibly complete) overlap between the set of epitopes comprising self and those expressed by

pathogens. Accordingly, mechanisms for the control of potentially autoreactive cells in the periphery after thymic selection are required. These are only just beginning to be delineated; the potential for cells present in the normal T cell repertoire to mediate autoimmune disease is highlighted in Chapter 11, as is the existence in the same repertoire of T cell subsets that are able to control the autoimmune effectors. This has been worked out mainly in relation to organ-specific immune disease (diabetes, thyroiditis) and, more recently, in inflammatory bowel disease, where it may be necessary to tolerate normal intestinal organisms as well as self (Duchmann *et al.*, 1995; 1996). However it is probable that similar mechanisms protect against rheumatic disease or are at fault when it occurs.

The exquisite sensitivity of immune recognition by immunoglobulins and T cell receptors has long fascinated immunologists, and how this is accomplished is now understood in great detail. However, since the process rests fundamentally on chance recombination events to generate receptors of the required specificity, the experience of successfully generating an antibody or T cell to deal with an important pathogen cannot be passed on from generation to generation: the functional receptor is not encoded in the germ-line, only the component genes required for the recombination process. The acquired ‘wisdom’ of the immune response that is germ-line encoded comprises the innate immune system, which does not require the generation of novel, highly specific receptors (Fearon, 1997). For example, receptors like those that bind mannose are useful for interactions with many bacteria, as are components of the complement system. Having been previously dazzled by the sophistication of the adaptive immune response, immunologists are now paying much more attention to the innate immune system, and in particular to its interactions with the adaptive immune response, which produces the best of both worlds. A good example is the ability of C3d, when complexed to antigen, to boost the antibody response by several orders of magnitude, so that tiny quantities of antigen are rendered immunogenic (Dempsey *et al.*, 1996). This effect depends on a complement receptor, CD21 or CR2; the family of complement receptors is reviewed in detail by Ahearn and Rosengard (Chapter 12), along with an account of how abnormalities in complement components and their receptors are likely to play a part in diseases such as SLE.

Concluding remarks

It can be argued that most rheumatic disorders occur in the context of an immune system that is generally competent – patients are able to protect themselves adequately from pathogens – but has some minor character defect that, as in all the best Greek tragedies, leads ultimately to disaster. These defects have not generally been defined but might include overexuberant responses to environmental

antigens in terms of the cytokines produced or the duration of response, or a crucial confusion between similar epitopes on foreign and self antigens. Our therapeutic response to these forgivable errors by the immune system has generally been to shut the whole system down to a substantial extent, with the inevitable consequence of vulnerability to the infectious agents. It is to be hoped that in future more subtle sanctions on the immune system, or a period of re-education, might have the desired effects on autoimmune/chronic inflammatory diseases, while maintaining intact defences against pathogens.

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