

AUTOIMMUNITY FOR THE GP

Autoimmunity remains an enigma.



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Years ago Ehrlich declared that it would be a catastrophe for the body to react against itself and called this 'horror autotoxicus'. It subsequently became clear, however, that self-reactivity/self-recognition was essential for normal functioning of the immune system, as well as a prerequisite for recognition of foreign organisms. Pathogens are only recognised by T-cells in the context of 'self' HLA molecules – termed HLA restriction. Indeed, HLA molecules play a vital role in immune recognition and in dictating the strength of an immune response. Many autoimmune diseases have strong HLA associations, e.g. type 1 diabetes (HLA DR3/4). Intense research efforts are currently directed at understanding the complex immune interactions leading to autoimmunity, in the hope that this will generate novel strategies for immune modulation and immunotherapy.

CURRENT CONCEPTS – IMMUNOPATHOGENESIS OF AUTOIMMUNITY

Autoimmune diseases are classified as either organ-specific (thyroid disease, type 1 diabetes, and myasthenia gravis) or non-organ-specific (systemic lupus erythematosus (SLE) and rheumatoid arthritis). Predisposing factors include genetic, hormonal (commoner in women), and HLA type, the disease being triggered by exposure to a variety of environmental factors such as viral infections and sunlight. This list of factors interacts in a complex immune network or 'mosaic' of autoimmunity. Differences in the exact combination present in any individual patient could explain the clinically diverse manifestations seen. For example, SLE can present simply as idiopathic thrombocytopenic purpura (ITP) or haemolytic anaemia, with disease expression limited to one organ for many years, or it can present with multi-system involvement of skin, renal, joints, and CNS. This kalei-

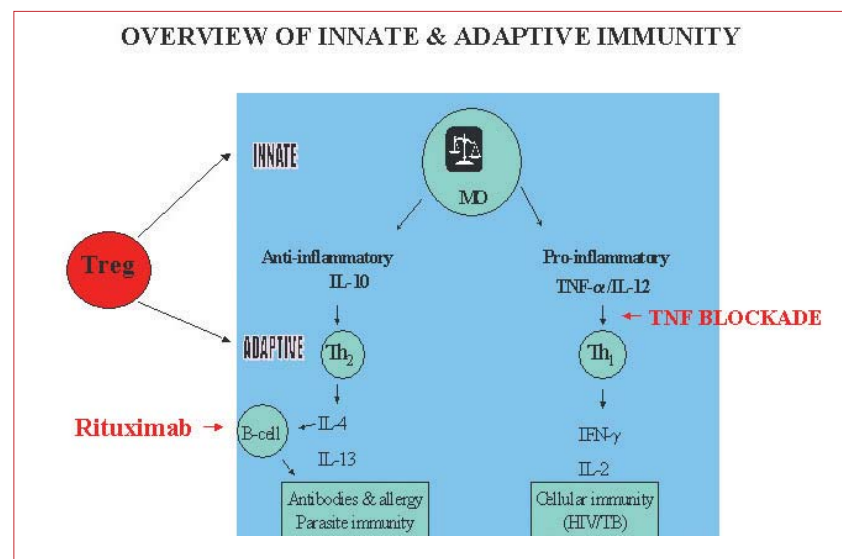


Fig. 1. Monocyte/macrophages control the balance of pro-inflammatory and anti-inflammatory responses through the cytokines they secrete in response to infection; they also dictate the nature of the subsequent adaptive immune response (see text). Treg are shown as a 'master regulator' controlling adaptive immune responses.

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doscope effect is due to variable clustering of the mosaic of predisposing factors in any individual, as first suggested by Schoenfeld and Isenberg over 20 years ago.

Tissue damage in most autoimmune diseases is mediated by autoantibodies and complement (e.g. Graves' disease, thyroiditis, SLE), but cellular immune effects are the predominant cause of pathology in others, such as type 1a diabetes. Adaptive immunity subdivides into 2 main types with distinct effector cells, secreted cytokines, and functions (Fig. 1).

This is largely determined by the cytokine dominance of antigen-presenting cells (APC: monocytes, macrophages and dendritic cells) which leads to the differentiation of opposite effector T-cells. Strong IL-12 secretion by APC favours induction of type 1 (Th-1) T-cells. Th-1 T-cells secrete interferon- γ and IL-2 cytokines, which are essential for protective immunity against intracellular pathogens, such as mycobacteria and HIV. However, proinflammatory Th-1 cells are also implicated in several organ-specific autoimmune diseases. Type 2 (Th-2) T-cells secrete IL-4 and IL-5 cytokines whose role is to protect against parasites and promote antibody production, but are also respon-

sible for allergy. Type 2 immune responses can also suppress type 1 proinflammatory T-cells. This can be utilised in immunotherapy.

Two major mechanisms are responsible for the induction of tolerance, namely central and peripheral tolerance induction. **Central tolerance** refers to the editing out of potential autoreactive T-cells during their development in the thymus, which explains why some 90% of thymocytes die at this stage of immune development. Some potentially auto-reactive T-cells do escape thymic deletion and these are held in check by a variety of **peripheral tolerance** mechanisms, which explains why autoimmunity is generally rare. Recent attention has focused on the critical role of a subset of naturally occurring regulatory T-cells (phenotypically identifiable as CD4+ CD25+), referred to as Treg, that function to regulate adaptive immunity (Fig. 1). Many organ-specific autoimmune diseases have been shown to have defective suppressor Treg function, including multiple sclerosis, rheumatoid arthritis, thyroiditis, and insulin-dependent diabetes. In type 1 autoimmune insulin-dependent diabetes, 'rogue' autoreactive T-cells mount an immune onslaught on islet cells, resulting in their progressive destruction in a delayed type of hypersensitivity (DTH) reaction. A number of autoantibodies are also found in the serum of these patients and their family members; these are directed at islet cells, glutamic acid decarboxylase (GAD), and/or insulin auto-antigens. In the latter case, these autoantibodies also serve as biomarkers in the pre-clinical phase that may predict future development of the disease, and have been the basis for trials using immunotherapy strategies to try and delay or prevent the disease. Detection of autoantibodies can also precede onset of clinical disease in several other autoimmune conditions. This offers the hope of early intervention where predictive values of the assays are high.

Autoimmune disease is then thought to arise from a failure of tolerance induc-

tion (defective Treg function), and through various mechanisms that serve to overcome or bypass tolerance (Table I).

Table I. Mechanisms through which overcoming tolerance results in autoimmunity

- Loss of peripheral Treg function – e.g. IDDM and RA
- Viral or drug-induced altered self-antigens – e.g. haemolytic anaemia
- 'Molecular mimicry' – cross-reactive antibodies, e.g. rheumatic fever
- Loss of 'sequestered' antigen or immunologically privileged status due to infection causing tissue damage and exposure of self-antigens to immune system

Most clinicians are familiar with 'molecular mimicry' mechanisms in the context of acute rheumatic fever, where antibodies directed at *Streptococcus pyogenes* in the throat cross-react with heart muscle antigens, causing carditis. T-cells are also involved in causing tissue damage through Th-1 type immune response. Thus, both Th-1 and Th-2 immune responses frequently co-exist and in most autoimmune disease, both contribute towards autoimmunity.

IMMUNOTHERAPY OF AUTOIMMUNITY

Corticosteroids and cytotoxic drugs remain the mainstay of therapy. Three additional approaches are briefly presented here.

In some diseases there is dominance of either Th-1 or Th-2 involvement (Table II).

This offers the possibility of therapy aimed at shifting the balance to the opposite subset, an immunomodulatory strategy that has been successful in animal studies and human autoimmune disease. For example, copolymer-1 (glatiramer acetate) treatment of patients with multiple sclerosis, a Th-1-

Table II. Th-1 and Th-2 involvement in some diseases

Th-1-associated autoimmunity	Th-2-associated autoimmunity
Rheumatoid arthritis	SLE
Multiple sclerosis	Graves' disease
Crohn's disease	Systemic sclerosis
Recurrent spontaneous abortions	Chronic graft v. host disease (GVHD)

associated disease, leads to peripheral Th-2 deviation. These Th-2 cells cross the blood-brain barrier and exert an anti-inflammatory and suppressive effect, which is believed to be responsible for the benefit observed in clinical trials.

Two further advances in immune-directed therapy arise from consideration of the immunopathogenesis illustrated in Fig.1.

TNF- α is a potent cytokine that has been implicated in chronic inflammation in several autoimmune diseases. The US FDA has approved 3 TNF- α blocking agents: etanercept (soluble TNF receptor fusion protein), infliximab and adalimumab (both anti-TNF monoclonal antibodies). In clinical trials they have been effective in the management of both longstanding and early rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Crohn's disease. They are being evaluated in clinical trials in other conditions, including Still's disease, Behçet's disease, uveitis and vasculitis. Of great interest is a recent study showing that response to anti-TNF therapy in patients with rheumatoid arthritis correlated with reversal of defective Treg suppressor function and a reduction in C-reactive protein levels. However, of concern are reported side-effects following anti-TNF treatment, including serious bacterial infections, reactivation of latent TB, opportunistic infections, and demyelinating syndromes. Great caution is therefore needed when using these biological response modifiers in South Africa, where TB is so prevalent.

Since autoantibodies are present in most autoimmune diseases, an attractive approach is to target B-cells directly. Rituximab is a monoclonal antibody

directed at a B-cell surface marker (CD-20) that demonstrated good efficacy in treating lymphoma. Several studies have now shown effective control of disease activity due to B-cell depletion by rituximab in both rheumatoid arthritis and SLE, particularly using combination therapy (with methotrexate, cyclophosphamide or steroids). There were no major side-effects and the use of rituximab is also being evaluated in several other autoimmune conditions.

UTILITY OF MEASURING SELECT AUTOANTIBODIES IN CLINICAL PRACTICE

Clinicians should keep in mind that interpretation of any assay depends on the pre-test probability of the test being positive. This in turn depends on the prevalence of the disease in any particular population, which affects the predictive value of the test.

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis

Antibodies directed at neutrophil cytoplasmic antigens are useful in the diagnosis of Wegener's granulomatosis (WG) and microscopic polyangiitis (MP). They are detected as 2 distinct patterns of fluorescence of ethanol-fixed neutrophils: cANCA (cytoplasmic) staining is found in WG, where the autoantibody reacts with proteinase-3-antigen. pANCA (perinuclear) staining is more commonly found in MP where autoantibodies react with myeloperoxidase. These antibody specificities can also be detected by ELISA assays. Current guidelines advocate that both methods be used for screening and confirmation. Relapses in patients whose disease is in remission may be heralded by a significant rise in ANCA titre, but the utility of monitoring ANCA titre routinely in

such patients is limited by the fact that disease relapse does not invariably follow a rise in antibody level. Furthermore, ANCA may be found in other conditions, such as infections. Careful consideration of the clinical presentation and histological evidence for vasculitis is therefore an essential prerequisite for embarking on immunosuppression.

Lupus serology

Antinuclear antibodies (ANA) remain a very sensitive screen for a variety of connective tissue disorders but lack specificity for SLE. Double-stranded DNA antibodies are highly specific for SLE but have lower sensitivity, as they may be transiently elevated and are particularly associated with immune complex nephritis. Anti-nucleosomal antibodies have recently shown promise as a better marker for SLE, and to correlate with disease activity. Their clinical utility is currently being assessed in clinical trials.

Antiphospholipid antibodies (APLA) are found in some patients with SLE or as a primary condition (APLA syndrome) with clinical presentations that include vascular thrombosis, thrombocytopenia, and recurrent, mid-trimester abortions. APLA are detected in coagulation screens as a prolonged PTT and/or in ELISA assays as antibodies to cardiolipin. APLA are a family of antibodies directed at several antigens, more recently antibodies to β 2GP1 (an anticoagulant serum protein) have been shown to be more specific.

Rheumatoid factor

Rheumatoid factor has low specificity for diagnosing rheumatoid arthritis, and can also be detected in chronic infections, especially infective endocarditis. As an indiscriminate screen in patients with arthralgia the test has low utility; it has been said that a thorough history and examination are the best screening tests. A new test involves detection of antibodies against citrullinated peptide (anti-CCP) that had > 80% sensitivity and > 90% specificity for diagnosing rheumatoid arthritis in several studies. Since the performance of this test shows greater specificity than rheumatoid factor, it

should provide useful diagnostic and prognostic information in patients presenting with early arthritis.

Autoimmune hepatitis (AIH)

This is a rare disease, the diagnosis of which has been facilitated by identification of novel autoantibodies in recent years, and it should be considered in any acute or chronic hepatitis of unknown aetiology. Two categories of AIH are described. Type I AIH occurs in young and middle-aged women who have other autoimmune features, hypergammaglobulinaemia, and high-titre circulating antinuclear antibody (ANA) or smooth-muscle antibodies (SMA), or both. Some patients also have antibodies to soluble liver antigens (SLA) or liver-pancreas (LP) antigen; these were previously thought to define a third type of AIH. Type II AIH can occur in young women or older men and is characterised by antibodies directed at liver-kidney microsomes (LKM). Taken together, these serological markers are helpful in distinguishing AIH from chronic viral hepatitis, which is clinically relevant since the treatment is different: steroids as opposed to interferon.

Antimyelin antibodies

The detection of serum antibodies against myelin basic protein (MBP) and oligodendrocyte glycoprotein (MOG) was shown to be highly predictive of a diagnosis of subsequent definite multiple sclerosis in patients with isolated neurological syndrome and abnormalities of the brain on MRI. This test is not routinely available and clinical utility needs to be confirmed in additional studies.

RECENTLY DESCRIBED AND/OR UNUSUAL AUTOIMMUNE DISEASES

Autoimmune pancreatitis

This is a controversial condition that has primarily been described in Europe and Japan. It may present in middle-aged men with jaundice, mild nonspecific abdominal pain, and weight loss. It enters into the differential diagnosis of diffuse pancreatic enlargement, needing to be distin-

guished from chronic pancreatitis, pancreatic cancer and lymphoma. It is an important diagnosis to make since it responds dramatically to steroids, and surgical intervention can be avoided. Diagnosis is made on the clinical picture, histological and radiological criteria, together with elevated IgG levels and the presence of auto-antibodies.

Autoimmune inner ear disease

This is a rare but potentially treatable cause of sensorineural hearing loss and vestibular symptoms, classically presenting in middle-aged women. Hearing loss is usually bilateral, occurs rapidly over weeks to months, can be accompanied by tinnitus and coexisting autoimmune diseases (rheumatoid arthritis, SLE, polyarteritis nodosa) and is thought to represent an autoimmune response to inner ear antigen. The diagnosis should be considered in patients presenting with a history consistent with bilateral Ménière's disease, where a positive autoimmune workup should lead to a trial of steroids. Methotrexate or other cytotoxic agents are sometimes required.

Primary immunodeficiency diseases

These diseases can have life-threatening autoimmune complications. Many of these conditions are rare, the commonest condition likely to be encountered by general practitioners (outside the paediatric age group) is common variable immunodeficiency (CVID) or late-onset hypogammaglobulinaemia. This presents with recurrent upper respiratory tract infections and/or chronic diarrhoea, the latter due to mucosal IgA deficiency resulting in GIT colonisation by *Giardia*. Commonly occurring autoimmune complications seen in these patients are rheumatoid arthritis, inflammatory bowel disease, autoimmune cytopenias and pernicious anaemia. These patients need to be managed by a multidisciplinary team that includes a respiratory physician, gastroenterologist, and clinical immunologist. The GP is pivotal in co-ordinating management.

Unexplained recurrent spontaneous abortion

There is a considerable literature documenting immune abnormalities in some women with recurrent spontaneous abortion. These include the finding of

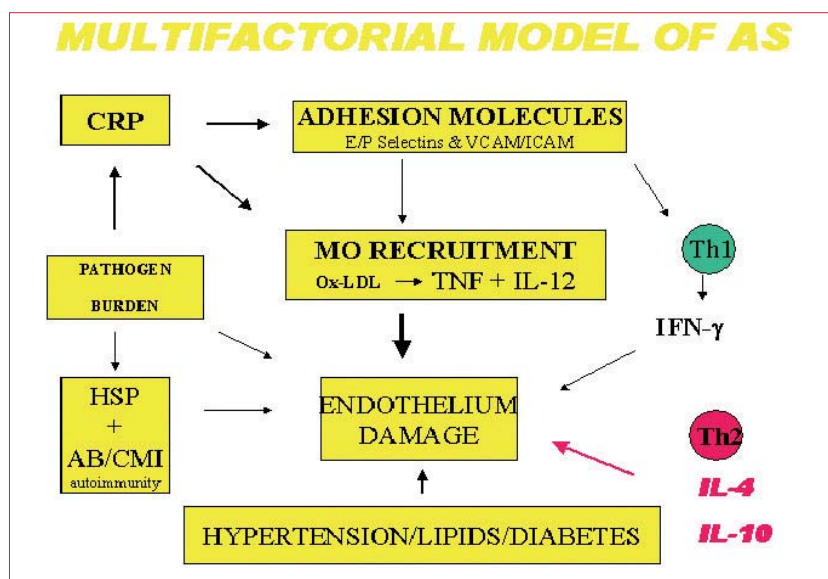


Fig. 2. Low-grade pathogen burden is thought to result in elevated C-reactive protein (CRP) levels that cause persistent inflammation. Auto-antibodies directed at heat shock protein (HSP-60), oxidised LDL, and β 2GPI have been detected in clinical studies; these can contribute to endothelial damage in conjunction with conventional risk factors (AS = atherosclerosis).

increased natural killer (NK) cell activity and elevated numbers of activated T-cells in the peripheral blood. Immunotherapy with injection of paternal leukocytes or intravenous immunoglobulin (IVIG) is claimed to improve the chances of successful pregnancy. This remains a controversial topic and many view such immunotherapy as experimental treatment that needs to be evaluated further in well-designed and ethically approved randomised control trials.

Chronic periaortitis (idiopathic retroperitoneal fibrosis)

This usually presents in men aged 50 - 70 with abdominal, flank or back pain, malaise, loss of weight, and anaemia. It has been thought to represent a local autoimmune response to lipoprotein antigens present in aortic atheromatous plaque. However, co-existing autoimmune disease such as SLE, primary biliary cirrhosis (PBC), RA, polyarteritis nodosa (PAN) or thyroiditis may also be present. It is important to diagnose (abdominal CT/MRI best) and responds to treatment with steroids and immunosuppressive agents.

Atherosclerosis

Although not a new disease, understanding of the pathogenesis of atherosclerosis has evolved through theories of a 'response to injury' hypothesis, 'altered lipoprotein' theory, to an immunological paradigm that incorporates an inflammatory process (raised C-reactive protein), infectious component (*Chlamydia pneumoniae*), and other autoimmune factors (Fig. 2).

CONCLUSION

Knowledge of autoimmunity continues to expand. Advances in our understanding of the molecular basis for well-described diseases provide new serological diagnostic tools, as well as novel targets for immunotherapy. The hope is that this will allow the design of more specific immunotherapeutic approaches that could avoid the side-effects associated with steroids, immunosuppressive and cytotoxic agents. The wide spectrum of diseases encountered poses a challenge to clinicians to recognise more unusual autoimmune presentations as well, despite their rarity.

References available on request.

IN A NUTSHELL

Autoimmunity results from the interaction of genetic and environmental factors, where immune regulation is defective.

Recent advances in understanding autoimmunity have provided new strategies for immunotherapy.

Patients with SLE have B-cell hyperactivity and respond to B-cell depletion with rituximab monoclonal antibody.

Inhibition of TNF- α has proved useful in patients with severe rheumatoid arthritis and Crohn's colitis, among other autoimmune diseases, but reactivation of TB is a serious concern related to this therapy.

Diagnosis of rheumatoid arthritis may be facilitated by a more specific assay – detection of anti-CPP antibodies.

Newly described anti-nucleosomal antibodies correlate with disease activity and detection of DNA antibodies in SLE.

Clinicians need to be vigilant for unusual presentations of autoimmunity since these patients respond to immune suppression; examples include autoimmune pancreatitis and chronic periaortitis.