



Review

Autoimmune diseases: Solution of the environmental, immunological and genetic components with principles for immunotherapy and transplantation

Duncan D. Adams^{a,*}, John G. Knight^b, Alan Ebringer^c^a Faculty of Medicine, University of Otago, Dunedin, New Zealand^b Faculty of Commerce, University of Otago, Dunedin, New Zealand^c King's College, University of London, United Kingdom

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ABSTRACT

Autoimmune diseases have environmental and genetic components. These are the microbial trigger, the immunity system component and the genetic component. Here we describe these components and how they interact. Known microbial triggers are *Streptococcus pyogenes* for rheumatic carditis, *Proteus mirabilis* for rheumatoid arthritis and *Klebsiella pneumoniae* for ankylosing spondylitis. The immunity system component has been clarified by realisation that no autoimmune disease is caused by loss of suppressor T cells. This leaves Burnet's forbidden clones, clearly seen in Graves' disease, as the immunological defect. With wide scope for clonal diversification by somatic gene mutations, to prevent frequent autoimmunity the immunity system is policed by the histocompatibility system. This dictates the immune response repertoire by deleting complementary clones (H Gene Theory). We show molecular evidence of how specific histocompatibility antigens can predispose to an autoimmune disease by influencing choice of the microbial antigen to which the immunity system reacts. Because of the unlucky random element in the somatic mutations involved in their development, forbidden clones are unlikely to reappear in new immune repertoires developing after immune ablation and autologous bone marrow cell reconstitution, as observed clinically. Isolation of autoantigens and their attachment to cytotoxic moieties could provide specific immunotherapy for autoimmune diseases. Kaplans's discovery that xenografts can be accepted without rejection after immune ablation followed by autologous and xenogeneic bone marrow inoculation, could enable widespread use of pig grafts for humans.

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* Corresponding author. Faculty of Medicine, University of Otago, PO Box 56, Dunedin, New Zealand. Tel.: +64 3 4877989.

E-mail address: duncan.adams@stonebow.otago.ac.nz (D.D. Adams).

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1. Introduction

Autoimmune diseases are caused by malfunction of the immunity system, being consequences of infection by bacteria or viruses [1,2]. Why do they occur? In Cecil's classical textbook of Medicine [3], it is stated repeatedly that environmental and genetic factors contribute to pathogenesis. It is now clear what these factors are and how they interact. This provides principles for immunotherapy and transplantation and will be described in this paper after outline of current knowledge of the microbial triggers.

2. Microbial triggers

2.1. Rheumatic carditis and streptococci

Before the advent of penicillin, rheumatic fever with crippling or fatal lesions of the heart was a frequent autoimmune complication of infections by β -haemolytic streptococci of Lancefield Group A. This was because of an antigenic similarity between components of the *Streptococcus* and heart tissue [4]. Today, with such infections therapeutically aborted by penicillin, rheumatic heart disease, once common, has virtually disappeared.

2.2. Glomerulonephritis and streptococci

Post-infective glomerulonephritis follows infection by Group A streptococci of multiple M types. This disease also is less frequent due to use of antibiotics.

2.3. Reactive arthritis

This has been observed after enteric infection with *Shigella*, *Salmonella*, *Yersinia* and *Campylobacter* and genital infection with *Neisseria gonorrhoea*.

2.4. Rheumatoid arthritis (RA) and *Proteus mirabilis* [5]

Multiple studies over three decades have found high titres of antibodies against this bacterium in a total of 1375 RA patients, but not in other diseases or healthy controls, in studies by independent groups in 15 different countries. There was no such elevation in

antibodies against 27 other microbial agents. There is evidence that the upper urinary tract is the main site of *Proteus* infection in RA.

2.5. Ankylosing spondylitis (AS) and *Klebsiella* [6]

In worldwide studies involving 1330 AS patients and 1191 healthy controls, the AS patients showed significantly increased antibody titres to *Klebsiella*. There is evidence that the gut is the main site of *Klebsiella* infection in AS.

2.6. Type 1 diabetes and Cocksackievirus

Richer and Horwitz [7] present the considerable evidence that Cocksackieviruses, especially B4, may trigger type 1 diabetes, including the discovery that there are shared regions of homology between the Cocksackievirus protein PC-2 and the islet antigen GAD65.

2.7. Systemic sclerosis and infections

Randone et al. [8] describe the evidence suggesting that Parvovirus B19, Cytomegalovirus, Epstein–Barr virus, Endogenous retrovirus or *Helicobacter pylori* infection might trigger systemic sclerosis, where it has been postulated that fibroblast-stimulating forbidden clones, probably of B cell origin, are the immunological agent [9].

2.8. Schizophrenia and virus infection

Acute schizophrenia has been observed to follow upper respiratory tract virus infections. Knight et al. have assembled much evidence indicating that schizophrenia is an autoimmune disease caused by autoantibodies that react with neuronal receptors influencing the limbic system [10–12].

3. The immunological component

3.1. Burnet's forbidden clone theory

Burnet postulated that unlucky mutations in multiplying lymphocytes generate what he aptly named the “forbidden clones” that cause the autoimmune diseases by reacting with a host antigen instead of an antigen on an invading microbe [13]. Strong experimental support comes from studies of Graves' disease [14], where the pathogenic

thyroid-stimulating autoantibodies (TSab) vary from patient to patient, showing a fine variation in specificity for antigen, demonstrable by presence or absence of reactivity with the various thyrotropin receptors of non-human animals. This indicates the random element in the lymphocyte somatic mutations involved in their generation [15].

3.2. The loss of suppressor T cells theory

As well as the helper T cells (thymus-derived lymphocytes) that stimulate B cell (bone marrow-derived lymphocyte) activity, there are suppressor T cells that inhibit immune activity. Allison et al. [16] postulated that loss of suppressor T cells is the cause of the autoimmune diseases, but purported evidence for this in New Zealand mice proved to be spurious [17]. Natchtigal et al. [18] proposed that immature T cells, meeting complementary antigen, differentiate into suppressor T cells, which suppress the specific immune response, in contrast to mature T cells, which become helper T cells. This regulatory function of T cells effectively controls the magnitude of an immune response, preventing it from continuing on until somatic mutations lead to leukemia or autoimmune disease. Hence, suppressor T cells are a vital element of the control of the immune system. In 1995, Sakaguchi [19], using lymphocyte cell-sorting technology and transfer of cells into lymphocyte-deficient mice, observed that animals deprived of suppressor (CD25+) lymphocytes develop autoimmune disease. Shevack [20] showed the existence of similar suppressor T cells in man and reflected on their enormous potential for therapeutic use, but noted that no way of achieving this has been devised.

3.3. Loss of suppressor T cells is not the cause of the autoimmune diseases

As Shevack observes, apart from a rare, lethal, genetic defect, no autoimmune disease has been identified whose pathogenesis is secondary to a deficiency of suppressor T cells. This leaves development of forbidden clones unchallenged as the cause of the autoimmune diseases. Fortunately, the technology needed for their selective destruction is already available, as described below.

3.4. Cytotoxic T cell forbidden clones

Sherwin's epic research on diabetes has been capped by his discovery that the exquisitely-specific destruction of the pancreatic islet β cells that causes type 1 diabetes is caused by cytotoxic T cells [21]. Following this up, Adams has postulated that antigen receptor related cytotoxic T cells destroy the retinal pericytes and that this is the cause of the vascular collapse of diabetic retinopathy [22], indicating the need for trial of immunotherapy.

4. The genetic components

4.1. The familial aggregation

Studies of families, including twins, show that autoimmune diseases are weakly inherited, with disease specificity, the Mendelian pattern being that of causation by multiple, codominant (expressed in the heterozygous state) genes with incomplete penetrance [9]. What genes are these? Before discussing this we need to describe the histocompatibility antigens, which were discovered in the field of surgical transplantation [23].

4.2. Functions of the major histocompatibility complex (MHC)

4.2.1. Defence against virus infection

Why do we have histocompatibility antigens? The main reason is for defence against virus infection. Zinkernagel and Doherty [24]

discovered that peptides from a virus infecting a cell are extruded to the cell's surface on a histocompatibility antigen molecule. There, the viral peptide is available for reaction with the antigen receptor of a cytotoxic T cell clone. If a reactive T cell clone exists, the virus-infected cell is destroyed. Why is the involvement of the histocompatibility molecule necessary? This is because of the explosive speed of virus replication [25]. In influenza virus infection, for example, as shown in Table 1, each virus-infected cell bursts open to release about a thousand virions, each of which infects a new cell, which in turn produces another thousand virions and so on. This huge number of virions would swamp the cytotoxic T cells, muffling their antigen receptors and so preventing them from destroying the virus factories that the infected cells become. It follows, that to prevent virus infections from being universally lethal, the defending cytotoxic T cell clones must be reactive with the conjoint virus-MHC antigen on the surface of the infected cells, rather than be reactive with the free virions.

4.2.2. The reason for powerful allograft rejection

Simonsen [26] discovered that we have huge clones of cytotoxic T cells reactive with other people's histocompatibility antigens. The natural function of these T cell clones is not to reject surgical allografts, but to roll over our own histocompatibility antigens, constantly checking for the presence of viral peptide, ready to destroy the cell if they find it. These cytotoxic T cell clones mistake allo-histocompatibility antigens on grafts for virus infection of host cells.

4.2.3. Involvement of the MHC in autoimmune disease

After Vladutiu and Rose [27] had discovered that the MHC influences occurrence of autoimmune disease in mice, Dausset and Svejgaard [28] reported that the human leukocyte antigens (HLA) are related to many diseases. Benacerraf and McDevitt [29] proposed that the major histocompatibility antigens are linked to immune response genes. However, such genes have not been found and it is now clear that it is the histocompatibility antigen genes themselves that are the immune response genes [9].

4.3. The H Gene Theory of inheritance of autoimmune disease

Building on the Bielschowsky's discovery of autoimmune anaemia in their NZB/BL strain of inbred mice, Howie and Helyer discovered that F1 hybrids of this strain with the healthy NZW strain, unexpectedly, develop the autoimmune kidney disease, lupus nephritis [30]. The occurrence of this disease in a hybrid, both of whose parents lack it, shows that at least one gene from each of the two parental strains causes the lupus nephritis. Back-cross and linkage studies of the New Zealand mice showed that three genes

Table 1

The reason for MHC presentation of viral antigen to cytotoxic T cells [25].

The contestants	Replication time	Progeny	
Influenza virus	10 h	1000 virions	
Cytotoxic T cell	18 h	2 lymphocytes	
The race	Virions	T cells	Virion:T cell ratio
Day 1	1	10^6	$1:10^6$
Day 2	$1 \times 1000^{2.4}$ $= 1.6 \times 10^7$	$10^6 \times 2^{1.3}$ $= 2.5 \times 10^6$	6:1
Day 3	2.5×10^{14}	6.5×10^6	$10^7:1$
Day 4	4.0×10^{21}	1.6×10^7	$10^{14}:1$

The result: the virus wins and the patient dies.

The conclusion: cytotoxic T cell clones need to be:

1. Large, preformed [26] (no time for expansion).
2. Specific for conjoint virus-MHC antigenic target, so as not to be muffled by the myriad numbers of free virions.

contribute to the lupus nephritis [31] and two to the autoimmune anaemia. The linkage studies showed that these are not the immunoglobulin V genes that were expected. Two are in the neighbourhood of the minor histocompatibility antigen genes, Hh and H-18. Putting together the research fields of autoimmunity and transplantation, Adams and Knight arrived at the H Gene Theory of inheritance of autoimmune disease [32]. This states that histocompatibility antigen genes, major, minor and HY (the male sex antigen), together with the V (variable region) genes coding for antigen receptors on B and T lymphocytes, are the germ-line immune response genes, the genes that influence the risk of autoimmune disease.

4.4. Addition to the immune repertoire by clonal deletion

Necessary for the H Gene Theory is the need for explanation on how histocompatibility antigens, by deleting complementary clones, can add to the immune repertoire. It was postulated that microbes bear multiple antigens and that a high affinity clone for one antigen will pre-empt reactivity by lower affinity clones for other antigens on the same microbe. Hence, histocompatibility antigens, by deleting certain clones, would cause others to be added to the immune repertoire and developed by somatic mutation, an alternative clonal development concept [9,25].

4.5. Molecular confirmation of the H Gene Theory in rheumatoid arthritis and ankylosing spondylitis

As shown in Table 2, Ebringer et al. [5] have demonstrated alternative clonal development in rheumatoid arthritis by showing that the triggering microbe, *P. mirabilis*, has two detectable antigens, a six amino acid sequence in the haemolysin with homology for HLA-DR1–4, the predisposing histocompatibility antigen, and a five amino acid sequence in the urease, with homology for collagen type X1, a likely autoantigen attacked. Because HLA antigens impose tolerance to themselves, people with HLA-DR1–4 will be unreactive to the haemolysin and therefore likely to react to the urease, starting a clonal development of lymphocyte mutations towards the forbidden clones that attack the joint collagen.

Similarly, Fig. 1 shows resemblance of the *Klebsiella* nitrogenase peptide to HLA-B27, which will protect the nitrogenase from immune reaction. The pullulanase peptide (Pul D) differs from the histocompatibility antigen by having a big, projecting tyrosine molecule and so is not protected from an immune reaction that can lead to development of a forbidden clone that causes ankylosing spondylitis [6].

4.6. Imperfect genetic protection against autoimmune disease

From generations of natural selection of H and V gene repertoires for reproductive advantage, histocompatibility (H) antigens protect from dangerous clonal developments, arising from V gene somatic mutations in lymphocytes that could lead to development of a

Table 2
Molecular similarities between *Proteus mirabilis* and self antigens [5], showing separate *Proteus* antigens for resemblance to the HLA sequence and for resemblance to the autoantigen attacked in rheumatoid arthritis, in accord with the H Gene Theory [32].

PROTEUS ANTIGENS	
Haemolysin	Urease
Glu-Ser-Arg-Arg-Ala-Leu	Leu-Arg-Arg-Glu-Iso
Glu-Gln-Arg-Arg-Ala-Ala	Iso-Arg-Arg-Glu-Thr
HLA-DR1/4	Collagen type X1
SELF ANTIGENS	

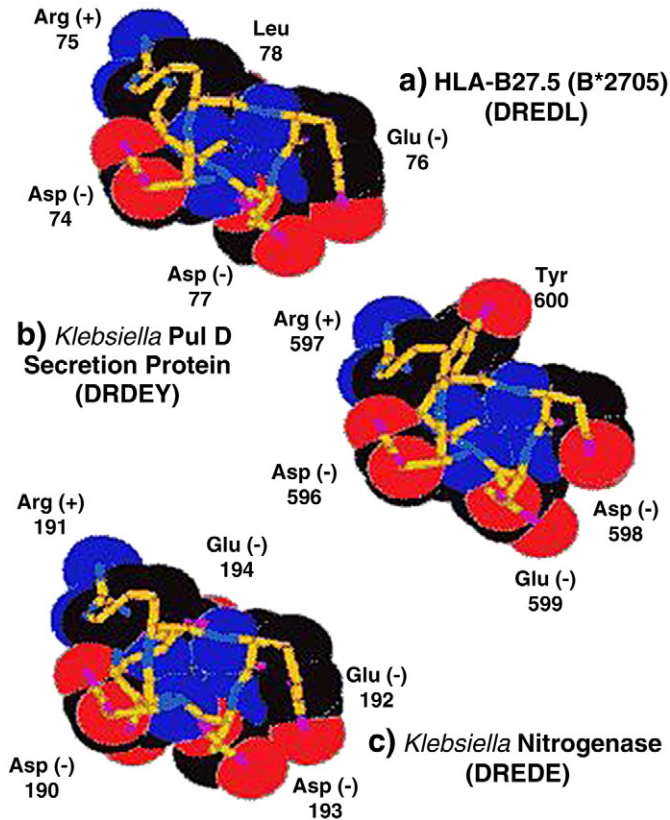


Fig. 1. Molecular similarity between HLA-B27 and the nitrogenase reductase peptide, and dissimilarity with the pullulanase peptide (Pul D), of *Klebsiella pneumoniae* [6]. This explains how HLA-B27 increases the risk of ankylosing spondylitis.

disease-causing forbidden clone. This explains all the genetic features of the autoimmune diseases [9,32]. The popular misimpression, that MHC genes predispose to autoimmune diseases, arises from the variable degree of imperfection of this protection, HLA-B27 and ankylosing spondylitis being one of the worst instances and HLA-DR 2 and type 1 diabetes being one of the best.

Mathieu et al. [34] describe the fascinating interplay between the 41 variants of HLA-B27 and relationship with malaria, illustrating the long-term natural selection of variants that have reproductive advantage.

4.7. A fourth category for McKusick's catalogue

In the light of the forbidden clone and H Gene Theories, the genetics of autoimmune disease changes from mystery, to elegant simplicity. The key is the random element imposed on the genesis of an autoimmune disease by the need for unlucky somatic mutations in lymphocyte V genes. Table 3 shows that autoimmune disease provides a fourth category to go with dominant, recessive and sex-

Table 3
Solution of the genetics of autoimmune disease.

A 4th category for McKusick's catalogue of Mendelian Inheritance [35].
1. Dominant. presence of the gene causes disease.
2. Recessive. absence of the gene causes disease.
3. X-linked. sex-linked, gene on X chromosome.
4. Autoimmune. Multiple codominant genes (V genes and H genes) with incomplete penetrance (due to need for antigenic triggers and somatic gene mutations in lymphocytes.) [32,33].

linked diseases in McKusick's catalogue of Mendelian inheritance in man [35].

5. Immunotherapy of autoimmune diseases

5.1. Generalized immune suppression

This is needed at present for many autoimmune diseases [3], using prednisone 40 mg/day for 3 weeks, tailing off to 5–10 mg/day for long-term maintenance without glucocorticoid toxicity.

5.2. Selective destruction of forbidden clones

5.2.1. Immune ablation and autologous bone marrow cell reconstitution

Following pioneering studies led by Tyndall [36], Englert et al. [37] recently saved the lives of three patients with systemic scleroderma of lethal severity. By the use of immuno-ablative chemotherapy, they got rid of their lethally-dangerous fibroblast-stimulating forbidden clones [9], then restored their immune systems with stem cells taken previously from each patient's own bone marrow [38]. Because pathogenic clones of B or T lymphocyte cells arise by unlucky somatic mutations in their V genes, during the multiplication of lymphocytes in the periphery [9], they are unlikely to reappear in the new, regenerated immune system. An alternative method for immune ablation is total lymphoid irradiation [39].

Other autoimmune diseases in which immune ablation followed by bone marrow reconstitution may be needed for severe cases, which include systemic lupus erythematosus, myasthenia gravis, Goodpastures' syndrome, diabetic retinopathy and nephropathy, and psychoses threatening suicide or murder.

5.2.2. Manufacture and use of cytotoxic autoantigen complexes

Ideal therapy for autoimmune diseases would be selective destruction of the pathogenic forbidden clones of lymphocytes, leaving the rest of the immune system intact. The research road towards this capability is now apparent [40]. It involves

- 1 Finding the forbidden clones. For seeking undiscovered ones, the receptor–ligand technology invented by GP Smith [41], with patients' serum or cerebrospinal fluid screened on bacteriophage peptide display libraries, is a good way to seek pathogenic autoantibodies, and could be modified for seeking T cell forbidden clones reactive with specific autoantigens.
- 2 Cloning the autoantigen. Vassart and Dumont's team [42] have cloned the TSH receptor, which is the autoantigen for Graves' disease. This has provided an autoantigen molecule that is used for measuring the thyroid-stimulating autoantibodies [43].
- 3 Attaching a cytotoxic moiety, such as bungarotoxin or ¹³¹Iodine, emitting short-range beta particles, then administering the molecular complex intravenously to destroy the pathogenic clones of plasma cells.

Such specific immunotherapy is not needed for Graves' disease, where excellent therapy is already available, but is needed for many other autoimmune diseases, including the psychoses. In rheumatoid arthritis (RA), Menard [44] has shown that some patients have autoantibodies to calpastatin. These autoantibodies may be pathogenic as calpastatin protects against excessive action of the proteolytic calpains that mop up extraneous protein fragments lost in the joint space. Edwards and Cambridge [45] have found evidence in support of this possibility by showing that depletion of B lymphocytes gave sustained improvement. Hence, in this subset of RA, manufacture and administration of cytotoxic calpastatin molecular complexes may be helpful and could pave the way for a similar therapy of other autoimmune diseases.

6. Transplantation

6.1. Chimera manufacture

HS Kaplan, a radiotherapist and researcher, who revolutionised the treatment of Hodgkin's disease [46], found that animals could be made into hematopoietic chimeras by total lymphoid irradiation followed by inoculation with allogeneic bone marrow, after which they could accept allogeneic skin and organ grafts from the donor of the bone marrow [47]. Full exploration of this neglected discovery could transform the field of transplant surgery.

6.2. Achievement of graft-tolerant and host-tolerant chimeras

Recently, Alexander et al. [48] brilliantly saved the life of a girl with liver failure from acute fulminant viral hepatitis. After receiving a mismatched liver allograft, and ingenious treatments, she eventually became a haematopoietic chimera, completely tolerant of her mismatched liver allograft.

The procedure for regularly achieving the needed graft-tolerant and host-tolerant chimera would seem to be the performance of immune ablation of the graft recipient, followed by inoculation with both autologous and donor bone marrow, before performing the allo-transplantation.

6.3. Pigs, the ideal organ donors

Being a domesticated meat animal of similar size to humans, pigs are ideal organ donors for providing kidneys, hearts and pancreatic islets for man. The problem of rejection should be removable by use of immune ablation and addition of pig bone marrow cells to the autologous bone marrow cell reconstitution, making the graft recipients human–pig hematopoietic chimeras. For reassurance before trial in man, Kaplan's studies could be repeated, as an urgent research necessity.

7. Discussion

Prevention is better than cure, so finding and countering antigenic triggers of autoimmune diseases is the ideal. The gold standard is set by penicillin, which aborts throat infections by β -haemolytic streptococci, and so has virtually abolished post-streptococcal rheumatic carditis, which used to kill or disable many people.

There was a false fear of pig xenografts on the basis of finding that a pig retrovirus could infect cultured human cells. However, pig heart valves have been used in hundreds of thousands of people in the USA, without trouble. The solution to the use of pig organ grafts without rejection problems would seem to be simple, namely to use Kaplan's procedure of immune ablation, with combined pig and recipient bone marrow cell immune reconstitution, to make patients the needed donor-tolerant and recipient-tolerant hematopoietic chimeras.

Much work lies ahead, but the pathways toward complete prophylactic or therapeutic conquest of the autoimmune diseases and unlimited transplantation from pigs without immune rejection complications, are becoming clear.

Take-home messages

- No autoimmune disease is caused by loss of suppressor T cells.
- Burnet's forbidden clone theory is correct, as demonstrated for Graves' disease.
- Because of the explosive speed of viral replication, MHC presentation of viral antigens to cytotoxic T cells is essential to direct the immune attack on to the surface of the infected cells, the virus factories.

- The bacteria triggering rheumatoid arthritis and ankylosing spondylitis both have two antigens, one protected by mimicry of a histocompatibility antigen, one resembling the autoantigen attacked, explaining MHC predispositions to autoimmune diseases, in accord with the H gene theory.
- Specific immunotherapy for autoimmune diseases can be achieved by immune ablation with autologous bone marrow cell reconstitution, and also by manufacture and use of cytotoxic auto-antigen complexes.
- HS Kaplan has shown how xenografts can be performed without rejection problems.

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Serum BAFF and APRIL in patients with PBC

B-cell activating factor belonging to the TNF family (BAFF) and a proliferation-inducing ligand (APRIL) are known to be involved in the occurrence of autoimmune diseases. In this study, Migita K. et al. (*Clin Immunol* 2010; 134: 217–25) assessed serum levels of these cytokines in PBC patients. Serum BAFF levels were significantly higher in PBC patients than in healthy controls (1253.9 ± 741.4 vs 722.8 ± 199.2 pg/ml; $p < 0.001$) and HCV-infected patients (1253.9 ± 741.4 vs 871.0 ± 251.1 pg/ml; $p = 0.015$). Whereas changes in serum APRIL levels were not significant among these groups, there was a significant correlation between BAFF and AST ($R = 0.278$, $p = 0.003$) or total bilirubin ($R = 0.363$, $p = 0.0006$) in PBC patients. Furthermore, serum BAFF levels were elevated in PBC patients with advanced interface hepatitis. This data indicate that serum levels of BAFF and APRIL are differentially regulated and serum BAFF levels are significantly elevated in PBC patients. These findings suggest that BAFF may serve as a modulator of the clinical and/or serological manifestation in PBC patients.