A B cell explanation for autoimmune disease: the forbidden clone returns

Fiona McQueen

ABSTRACT
More than 60 years ago, Burnet first proposed the ‘forbidden clone’ hypothesis postulating that autoimmune disease arises as a result of persistence of self-reactive clones of lymphocytes that should have been deleted via immunological tolerance. These autoreactive clones could effect immune-mediated end-organ damage via peripheral self-antigen recognition. Recent evidence that stretches across the boundaries of many medical specialties supports this proposal, implicating a B cell precursor as the culprit. The success of B cell depleting therapy in rheumatoid arthritis, anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis, polymyositis, lupus and autoimmune diseases as diverse as multiple sclerosis and idiopathic thrombocytopenic purpura supports this proposal. Clonality of B cells and plasma cells has been described in a number of autoimmune disorders and the presence of autoantibodies, which may arise years before the onset of clinical disease, supports the notion of autoreactivity within the B cell lineage. T cell activation within the end-organ would be predicted by cognate B–T cell interactions and resultant tissue inflammation and destruction could produce diverse clinical manifestations dictated by the original specificity of the autoimmune B cell.

INTRODUCTION
In 1960, Sir Frank McFarlane Burnet was awarded the Nobel Prize for Medicine and Physiology for his work on the immunological recognition of self. His ‘forbidden clone’ hypothesis proposed that autoimmune disease develops as a result of persistence of self-reactive clones of lymphocytes that should have been deleted via normal immune tolerance. These autoreactive clones multiply and effect immune-mediated end-organ damage via peripheral self-antigen recognition. He suggested that clones might arise as a result of somatic mutation early in lymphoid differentiation. This proposal antedated the recognition of T and B lymphocyte subsets at a time when immunologists were focused on the role of autoantibodies such as the long-acting thyroid stimulator antibodies, which produce Grave’s disease. However, in the latter part of the 20th century, T cells dominated theories of autoimmunity and B cells were largely relegated to the sidelines with autoantibodies being regarded as epiphenomena. During the same period, the care of patients with autoimmune diseases devolved to quite separate groups of medical specialists, leading to compartmentalisation and loss of an overarching perspective.

A sea change is now occurring and interest in B cells is on the rise. This has been catalysed by the success of B cell depletion therapy (BCDT), particularly in rheumatoid arthritis (RA), but also in other autoimmune diseases ranging from systemic lupus erythematosus (SLE) to polymyositis to idiopathic thrombocytopenic purpura (ITP). This review aims to draw together several lines of evidence indicating that a defect in B cell tolerance could directly contribute to the onset of autoimmune disease. A summary of the clinical efficacy of BCDT is presented initially and then the proposal is systematically examined from a number of viewpoints including B cell developmental biology and where a ‘forbidden clone’ might arise, the genetics of autoimmunity and possible role of regulatory transcription factors, evidence for B cell and plasma cell clonality at a tissue level, the association between autoimmunity and lymphoma and how autoantibodies predate the onset of clinical autoimmune disease. The role of T cells, human leukocyte antigen (HLA) antigens and cytokines as ‘codefendants’ in taking immune dysregulation to a fully fledged autoimmune disease is then addressed.

B CELL DEPLETION IS EFFECTIVE IN AUTOIMMUNE DISEASE
BCDT has recently been shown to be effective in a wide range of autoimmune diseases (table 1). Interest in BCDT within the rheumatology community was sparked by the pivotal work of Edwards et al who used a lymphoma regimen including the B cell depleting anti-CD20 monoclonal antibody, rituximab, to treat severe long-standing RA. Recent large clinical trials now place rituximab in the mainstream of RA therapy. This drug is highly effective for suppressing joint inflammation, is also potently antierosive and has recently been shown to suppress MRI bone oedema (reflecting osteitis) as well as synovitis. Efficacy has also been demonstrated in primary Sjogren’s syndrome (pSS). In SLE, two large clinical trials have not shown BCDT to be superior to conventional management but nonetheless many patients are being treated off label, especially where standard therapies fail, as there is evidence of efficacy from observational studies. The recent success of belimumab, a humanised monoclonal antibody that inhibits B lymphocyte stimulator, also known as B cell activation factor of the tumour necrosis factor family (BAFF), underlines the role of B cell autoimmunity in lupus. BCDT also has important efficacy in the antineutrophil cytoplasmic antibody (ANCA)-related vasculitides including Wegener’s granulomatosis, despite the formation of granulomata traditionally being
ITP9 to Grave

spectrum of non-rheumatic autoimmune diseases ranging from interactions. Fascinatingly, BCDT is also effective in a wide interfering with antigen presentation to preventing cognate T
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ascribed to T1-helper cell-mediated immunity. Whole theories of disease pathogenesis are having to be reworked as conditions classically attributed to T cell autoimmunity such as poly-
ymyositis also prove in many cases to respond to BCDT. Where exactly BCDT exerts its influence remains obscure, and possibilities range from abrogating autoantibody production to interfering with antigen presentation to preventing cognate T–B cell interactions. Fascinatingly, BCDT is also effective in a wide spectrum of non-rheumatic autoimmune diseases ranging from ITP to Grave’s disease to multiple sclerosis, where a recent study provided class III evidence that add-on rituximab reduced gadolinium-enhancing MRI brain lesions. Rituximab has also been shown to protect pancreatic islet function in type 1 diabetes.

**B CELL DEVELOPMENT: THE FORBIDDEN CLONE**

In the light of the success of BCDT, it is now time to review the forbidden clone hypothesis as a possible explanation for the genesis of autoimmune disease from a B cell perspective. Could a very early cell in the B lymphocyte lineage acquire autoimmune potential and act as a first trigger? Such a cell might be among the immature B cells developing within the bone marrow (figure 1A). During B lymphocyte development, surface light and heavy chains assemble to form the B cell receptor (BCR). Random gene segment rearrangement occurs, especially within the complementarity determining regions of variable regions, to produce antibodies with a vast number of specificities with which to arm a competent immune system. Negative and positive selection operate during B cell development, shaping the mature B cell repertoire. Negative selection of B cells has been investigated extensively in mice where the pre-BCR appears to censor the development of autoantibody-secreting cells. Goodnow et al used a double transgenic model to study the development of autoimmune B cells. These animals were engineered to express a gene for a neo-self antigen, hen egg lysozyme and also to produce B cells that generated high affinity

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Level 1: Evidence obtained from at least one properly designed randomised controlled trial.

Level 2: Cohort or case-control studies or dramatic results from uncontrolled trials.

ACPA, anticitrullinated peptide antibodies; anti-dsDNA, anti-double stranded DNA antibodies; BCDT, B cell depletion therapy; IAA, insulin autoantibodies; ICA, islet cell autoantibodies; IDDM, insulin dependent diabetes mellitus; ITP, idiopathic thrombocytopenic purpura; neg, negative; NHL, non-Hodgkin’s lymphoma; NOD, non-obese diabetic; pos, positive; pSS, primary Sjögren’s syndrome; PTPN22, protein tyrosine phosphatase, non-receptor type 22 (lymphoid); RA, rheumatoid arthritis; SIR, standardised incidence ratio; SLE, systemic lupus erythematosus; STAT4, signal transducers and activators of transcription-4; Tg, thyroglobulin; TPO, thyroperoxidase; TSHR, thyroid stimulating hormone receptor.

Evidence available suggests the effect or association is weak (+), moderate (++), strong (+++) or not observed (−).

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Figure 1 Hypothetical pathway for escape of an autoimmune B cell from normal tolerance controls. (A) A precursor B cell expresses an early B cell receptor. This cell has autoimmune potential as it recognises self-antigen peripherally. (B) A mutagenic event occurs in genetic sequences regulating immune tolerance in precursor B cell with autoimmune potential so that it is not deleted. (C) Autoreactive B cell clones develop in bone marrow and form plasma cells which release autoantibodies. (D) Autoantibodies mediate autoimmune disease via several pathways including receptor stimulation (Grave’s disease), complement-mediated tissue damage (systemic lupus erythematosus) or T cell activation (rheumatoid arthritis).
antilysozyme antibody. B cells bearing the self-BCR died after 1 day in the bone marrow (by apoptosis) following encounter with the self-antigen, consistent with clonal deletion. Fang et al took this model a step further and transfected transgenic animals with a bcl-xL death inhibitory gene.55 The B cells that should have been autoreactive were ‘saved’ and proliferated normally, but were anergic to the autoantigen (hen egg lysozyme) in the periphery. Thus, autoreactive B cells that escape clonal deletion may be rendered anergic as part of normal immune tolerance.

B cell development differs to some extent in humans and Wardemann et al studied single B cells from the bone marrow and blood of healthy human donors and cloned antibodies from them.52 They found that 76% of antibodies cloned from early immature B cells displayed self-reactivity, including antinuclear specificities. This was especially apparent in antibodies with long or highly positively charged immunoglobulin (lg) heavy chain complementarity determining regions. The frequency of self-reactive clones then fell to 45% in the late immature B cell stage, remained at 41% in B cells newly emigrated into the peripheral blood and then dropped further between the ‘new emigrant’ and naive B cell stages. It is fascinating to note that CD20 is acquired at the immature B cell stage in light of the efficacy of rituximab in autoimmune disease, particularly if this is a major checkpoint for negative selection of autoreactive cells.52 These authors concluded that inefficient checkpoint regulation would lead to substantial increases in circulating autoantibodies with the potential to trigger autoimmune disease.

If autoantigen-binding B cells do escape deletion and migrate to the periphery, they compete poorly with naive B cells and rapidly undergo cell death.56 These autoreactive B cells are highly dependent on cytokines such as BAFF for their survival.56 Thus, under conditions where BAFF levels are high, autoreactive B cells may be allowed to survive. Interestingly, high BAFF levels do occur in a number of autoimmune diseases and BAFF is expressed at inflammatory sites where there is lymphoid neogenesis.52

Transgenic mouse models expressing high levels of BAFF demonstrate similar signs to those observed in SLE and Sjoøgren’s syndrome.58 Taken together, these lines of evidence imply that powerful intrinsic controls are in place to prevent the escape of active autoimmune B cells to the periphery. Multiple checkpoints exist to maintain B cell immune tolerance and if one or more of these failed, for example, due to mutation within a regulatory gene in the setting of an abnormal cytokine environment, the stage might be set for the development of autoimmune disease.

GENETICS: A COMMON AUTOIMMUNE BACKGROUND

What is very interesting about the genetics of autoimmune disease is that susceptibility genes seem remarkably conserved across a broad spectrum of clinical conditions. Such genes include the protein tyrosine phosphatase FTPN22 gain-of-function variant, Trp620, which is associated with type 1 diabetes.36 RA, autoimmune thyroid disease, ITP and SLE.52 Variants of the signal transducers and activators of transcription-4 (STAT4) genes on chromosome 2q have also recently been associated with SLE and RA.53 Sjoøgren’s syndrome,54 systemic sclerosis,55 and type 1 diabetes.57 Similarly, CTLA4 and FCRL3 have been reported to associate with several autoimmune conditions including RA, SLE and autoimmune thyroiditis.60 Many of these genes are involved in the regulation of T and B cell activation and differentiation. Remmers et al proposed that ‘common risk genes underlie multiple autoimmune disorders and suggest common pathways of pathogenesis.53 Monogenic inherited defects such as the forhead box F3 (FOXE3) gene mutation are known to affect T cell tolerance.62 FOXP3 plays a crucial role in the development and function of regulatory T cells and mutation of this gene is associated with the very rare immunodeficiency, polyendocrinopathy and enteropathy X linked (IPEX) syndrome.63 Similarly, hereditary mutation within the autoimmune regulator (AIRE) gene interferes with expression of proteins in the thymus that govern T cell tolerance. This leads to the rare recessive disorder entitled autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy.64 While neither of these genes is associated with common autoimmune disease, SLE patients do exhibit relative dysfunction of FOXP3 positive cells.65 T and B cell cooperation is apparent in the developing and mature immune system and although not yet described, genes controlling the development of B cell tolerance are also highly likely to predispose to autoimmunity. The current proposal would suggest that somatic mutation of one of these genes at a key regulatory point in B cell development could set the stage for autoimmune disease.

REGULATORY GENES IN THE MYELOPROLIFERATIVE DISORDERS

How could one genetic mutation in a regulatory gene set the scene for such a wide variety of autoimmune diseases? This is now well recognised to occur in myeloproliferative diseases (MPDs) where a gain-of-function mutation occurs in the pseu

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lymphoid follicles in Sjogren’s syndrome and Hashimoto’s thyroiditis and also in peripheral blood from patients with idiopathic thrombocytopenic purpura (ITP) and bone marrow from RA patients. Sfiakakis et al described peripheral B cells harvested from patients with active lupus as containing clonally-related Ig-VH/DH/JH sequences suggesting expansion of single B-cell precursors with clonal evolution. Similar structures have recently been reported by Chang et al in more than half of 68 lupus nephritis biopsies. Recently, Scheel et al found large plasma cell clones in rheumatoid synovial tissue. They isolated B cells and plasma cells, extracted their RNA, and amplified, cloned and sequenced the Ig VH genes. Certain V–D–J rearrangements were isolated repeatedly and these B cells and plasma cells with an identical rearrangement and pattern of somatic mutations were found within lymphoid infiltrates. There was evidence for Ig class switching and intraclonal diversity which would result in the formation of antibodies of multiple specificities. Plasma cells have also been found in rheumatoid bone within the osteitis lesion where MRI scans revealed bone oedema. Clonality has yet to be demonstrated at that site but plasma cell numbers were highly correlated with the number of osteoclasts sitting adjacent to bony trabeculae suggesting an activator–effector partnership.

AUTOIMMUNE DISEASE AND MALIGNANCY

One could speculate that indolent lymphoproliferation could occasionally be followed by transition to frank malignancy, as occurs in the MPDs, where transition to acute myeloid leukaemia may occur. If one assumes the cell of origin in autoimmune disease to be the B lymphocyte, then association with B cell non-Hodgkin’s lymphoma (NHL) would be predicted. Indeed, B cell NHL is associated with various autoimmune diseases, with standard incidence ratios highest in Sjogren’s syndrome at 18.8 in one meta-analysis but also raised in SLE (7.4) and RA (3.9). Associations have also been described with autoimmune thyroid disease and (debatably) insulin dependent diabetes mellitus (table 1). Authors have

Figure 2  B cells and plasma cells are found associated with T cells in peripheral tissues of patients with autoimmune disease. (A) Lymphoid follicular structures: clockwise from top left: rheumatoid synovium (Ed Klatt MD, WebPath), rheumatoid periarticular bone, salivary gland from a patient with Sjogren’s syndrome (Dr M Dray, Dept Pathology Middlemore Hospital, Auckland, New Zealand) and thyroid gland from patient with Hashimoto’s thyroiditis (Dr M Dray, Dept Pathology Middlemore Hospital, Auckland, New Zealand). (B) Cognate B–T cell interactions: B cells internalise antigen, process and present (via Class II antigens in the presence of costimulatory molecules) to T cells via their cognate receptor. This produces T cell activation and proliferation. (C) Active inflammatory lesion develops. (D) End-organ damage occurs with eventual loss of function. IL, interleukin, RANKL, receptor activator of nuclear factor κ B ligand; TNFα, tumour necrosis factor α.


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proposed that prolonged auto-antigenic stimulation from within the organ in question drives this predisposition to malignancy, which would in fact be consistent with the hypothesis proposed here.

An alternative hypothesis suggests that a persistent infectious agent may precipitate autoimmune disease and this in turn could lead on to malignancy, again via prolonged antigenic stimulation. The Epstein-Barr virus (EBV) is an attractive candidate in view of its propensity to replicate within B cells, inhibit apoptosis and transform cultured B cells into lymphoblastoid cell lines. Sequence homology between self-antigens of relevance in SLE and pSS and EBV proteins has been recognised and EBV is capable of inducing an immune response against citrullinated proteins in RA. However, much of this evidence is circumstantial and the observation that the EBV load is higher in patients with RA, SLE and pSS could represent an epiphenomenon related to abnormal immune regulation in autoimmune disease. The strongest association between autoimmune disease and NHL occurs in pSS but there the association with EBV remains tenuous. In one study of 16 pSS patients with lymphoma, no association was found between EBV positivity of biopsied salivary glands and EBV positivity of lymphoma.

Thus, while infection cannot be excluded as a trigger for neoplasia in some circumstances, it is not an adequate explanation for the association between autoimmunity and NHL overall. The hypothesis described here proposes that a somatic mutation occurring within a checkpoint controlling the elimination of autoimmune B cells leads ultimately to autoimmune disease. A further mutation event, or second hit, could occur at sites of lymphocytic proliferation and lead on to frank malignancy. Rituximab is an established therapy for NHL and it is interesting that reports have documented its efficacy in treatment of MALT lymphomas with a concomitant beneficial effect on associated autoimmune disease such as Sjogren’s syndrome.

THE ROLE OF AUTOANTIBODIES

If a B cell precursor is implicated in the genesis of autoimmune disease, autoantibodies should be detectable and play a causative role in the clinical manifestations of disease (figure 1D). This is certainly the case for ITP (platelet-depleting antibodies) and very likely to be true for SLE (anti-double stranded DNA antibodies) and necrotising vasculitis (anti-neutrophil cytoplasmic antibodies (ANCA)). In RA, highly specific anticitrullinated peptide antibodies are associated with overt clinical disease and detectable 9 years and more before the onset of symptoms. Similar findings characterise type 1 diabetes as patients with insulin autoantibodies and islet cell cytoplasmic autoantibodies have >90% probability of developing diabetes within 6 years. Autoantibodies have also been shown to precede the onset of lupus with anti-double stranded DNA antibodies appearing 2.2 years before diagnosis in a study of US armed forces personnel. This has also been described for autoimmune thyroid disease in a similar large cohort of military personnel. In scleroderma, potentially stimulatory autoantibodies to endothelin-1 receptor and anegetoisin II type I receptor have recently been described and provide a putative explanation for vasoreactivity and pulmonary hypertension.

Could clonal evolution as described in the MPDs play a part here? In these disorders, mitotic recombination is thought to account for transformation from a heterozygous Jak2 mutation to a homozygous state associated with a survival advantage and more aggressive clinical disease. In autoimmunity, one could postulate the existence of a clone of B cells within the bone marrow producing a relatively innocuous autoantibody for many years before transforming, possibly by epitope spreading, to a clone which elaborates a slightly different autoantibody, now capable of producing peripheral tissue destruction.

T CELLS AND HLA ANTIGENS

How would a B cell theory of autoimmunity fit with the indisputable role played by T cells in diseases such as RA? The shared epitope hypothesis implicates the T cell in view of its interaction with antigen presented in the context of disease-associated Class II HLA subtypes. This would still be relevant in a B cell driven scenario, both very early on at the time of the autoimmune B cell’s escape from deletion (which is driven by self-antigen presentation, figure 1A) and late in the disease process when B–T cell interactions are occurring in the periphery (figure 2). Some HLA molecules are associated with a strong susceptibility for one autoimmune disease but confer protection against another (eg, DQ6 is associated positively with multiple sclerosis but negatively with insulin dependent diabetes mellitus), suggesting that in some individuals, the wrong HLA type cannot present this triggering antigen leading to protection from autoimmune disease. The study by Berglin et al, who examined pre-RA blood donor samples, is entirely consistent with this part of the B cell hypothesis. They found that anti-CCP positivity gave an OR of 25.1, and the combination of anti-CCP antibodies and shared epitope gene carriage gave an OR of 66.8 for the risk of later developing RA.

B–T COSTIMULATION

Clearly B cells have a major role in stimulating T cell activity via cognate interactions as well as non specifically by acting as antigen-presenting cells (APCs). Abatacept, a CTLA4-Ig fusion molecule that blocks B cell driven costimulation of T cells, is effective in reducing inflammation and suppressing erosion in RA. T cells are likely to be on the effector side of the relationship as the T cell derived receptor activator of nuclear factor κ B ligand (RANKL) activates osteoclasts and is likely to drive bone erosion. In the thyroid, Battifora et al noted that intra-thyroidal T cells were responsive to the B7 ligand, CD28. This would fit with the same B–T cell scenario driving tissue damage in the target organ as occurs in RA. Pharma companies are sufficiently interested in these possibilities to institute large multicentre trials of co-stimulatory blockade in other autoimmune diseases, including the A Cooperative Clinical Study of Abatacept in Multiple Sclerosis (ACCLAIM) study, investigating abatacept in multiple sclerosis (currently recruiting). If the T cell was the initiator of the autoimmune process then T cell depletion should be also effective but these agents have uniformly

Main messages

- Strong evidence exists implicating B cells in autoimmune disease.
- Escape of an autoimmune B cell precursor from normal tolerance could be the initial step.
- The antigenic specificity of this B cell would dictate the organ affected.
- There is evidence for B cell and plasma cell clonality in several autoimmune diseases.
- Further studies of B cell depleting therapy are warranted in autoimmune disease, targeting specific B cell precursors.
failed to be effective in RA and elsewhere. Thus, biological agents that target specific molecules and pathways can be used to ‘unpick’ the riddle of autoimmunity.

ORGAN BASED DAMAGE: INFLAMMATION AND CYTOKINES
At the level of the target organ, an inflammatory infiltrate is present in many autoimmune diseases featuring B and T lymphocytes, plasma cells, macrophages, dendritic cells, fibroblasts and proliferating small blood vessels. The B cell hypothesis would predict that the target antigen would be found there, as citrullinated peptide antigens are found in the RA synovial membrane and thyroglobulin within thyroid follicles. Interaction with appropriately active T cells would then occur as has recently been demonstrated with vimentin in RA and release of cytokines could trigger tissue damage via a type II hypersensitivity response. Production of antigen–antibody complexes may also occur with complement consumption and a type III hypersensitivity response resulting in vasculitis or glomerulonephritis. Diverse clinical manifestations could then ensue ranging from SLE to RA to autoimmune thyroid disease, dictated by the function of the cells/organs being damaged (figure 2). Proinflammatory cytokines such as tumour necrosis factor α (TNF α) play a major role in promoting tissue damage, hence the effectiveness of anti-TNF agents which are now used across a broad spectrum of disease.

CONCLUSION
In summary, autoimmune diseases could be viewed as indolent lymphoproliferative disorders of B cell origin where a cell with autoimmune potential escapes deletion, possibly due to a mutation in a regulatory gene controlling a crucial checkpoint that maintains tolerance. As it has escaped normal homeostatic mechanisms, this cell is permitted to proliferate, differentiate and as a plasma cell, produce its relevant autoantibody. This could directly affect the target tissue or could act in concert with T cells and APCs to produce organ damage. Evidence for this hypothesis is strong from genetic and immunopathological studies and, most convincingly, from the efficacy of BCDT in many of these conditions. However, this is still a ‘broad brush’ explanation and unanswered questions remain. Why for example were the clinical trials of BCDT in lupus largely negative? What would be the effect of targeting a different set of B cell precursors (as is now underway in lupus trials)?

SELF ASSESSMENT QUESTIONS (ANSWERS AFTER THE REFERENCES)
1. Variants of the PTPN22 gene have been associated with the following diseases except one:
   A. Rheumatoid arthritis
   B. SLE
   C. Primary Sjogren’s syndrome
   D. Hashimoto’s thyroiditis
   E. Type 2 diabetes

2. The strongest association between B cell NHL and an autoimmune disease is for which one of the following?
   A. Rheumatoid arthritis
   B. SLE
   C. Primary Sjogren’s syndrome
   D. Hashimoto’s thyroiditis
   E. Type 2 diabetes

3. Ectopic lymphoid neogenesis has been described in all of the following except which one?
   A. Rheumatoid arthritis
   B. SLE
   C. Primary Sjogren’s syndrome
   D. Hashimoto’s thyroiditis
   E. Idiopathic thrombocytopenic purpura

4. B cell depletion therapy has been shown to be effective in controlled clinical trials in which one of the following?
   A. Thrombotic thrombocytopenic purpura
   B. Rheumatoid arthritis
   C. SLE
   D. Mixed connective tissue disease
   E. Pemphigus
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