Pathogenesis of Primary Biliary Cirrhosis

David E.J. Jones, MD, PhD

Liver Research Group, Institute of Cellular Medicine, The Medical School,
Newcastle University, 4th Floor, William Leach Building,
Framlington Place, Newcastle-upon-Tyne, NE2 4HH, United Kingdom

Primary biliary cirrhosis as a landmark disease

Primary biliary cirrhosis (PBC) has acted, in many ways, as a landmark disease for establishing concepts regarding the pathophysiology of conditions in which autoimmune phenomena are prominent. PBC was one of the first diseases in which the presence of serum autoantibodies was recognized [1]. Likewise, it was one of the first diseases in which the identity of key autoantigens was established [2]. Understanding of the pathogenesis of PBC and, in particular, the precise role played by autoreactive immune responses remains, however, incomplete, with increasingly contradictory observations made in recent years. PBC is continuing, it seems, to act as a landmark disease by demonstrating that the pathogenesis of apparently autoimmune diseases is significantly more complex than the initially simplistic models might have suggested [3]. PBC acts as a landmark disease in one other highly clinically relevant way by demonstrating that detailed understanding of autoimmune phenomena does not, as perhaps naively originally believed, lead inevitably to improvement in therapy. This lesson is starting to be learnt in other autoimmune diseases. The aim of this article is to present a contemporary perspective of the pathogenesis of PBC, to discuss the currently proposed models, and to draw realistic conclusions regarding where the current understanding of disease pathogenesis is likely to lead in terms of therapy in the near future.

Key clinical observations that may guide understanding of primary biliary cirrhosis pathogenesis

When considering the individual pathogenetic models for PBC, it is useful to remember the key clinical observations that characterize the disease (and which are, on occasion, overlooked in developing the concepts of
pathogenesis). For any particular model to be valid, it must be able to explain, or at least be able to account for, each of these key clinical observations (Tables 1–3). It is sobering to realize that, in reality, none of the pathogenetic models proposed for PBC is able to truly account for all these key clinical observations.

Autoantibody

Autoantibodies frequently are seen in patients who have PBC and, typically, are present at very high titers. The universal finding of autoantibodies and associated autoreactive phenomena (discussed later) in patients who have PBC demonstrates the presence of self-directed immune responses in this disease. The key question is whether or not the presence of such responses represents autoreactivity (the presence of immune responses directed at self-antigens) or true autoimmunity (autoreactivity resulting directly in target cell damage and the induction of pathology). Any model based on autoreactive antibody responses playing a key role must be able to account for the development of disease in the small, but clearly delineated, subgroup of patients who have autoantibody-negative disease (described in detail in the article by Muratori and colleagues elsewhere in this issue).

Elevated serum IgM

Most patients who have PBC exhibit polyclonal elevation in serum IgM, which is typically not directed at mitochondrial or nuclear antigens [4]. At face value this phenomenon is suggestive of polyclonal activation of the B-cell compartment, with an associated failure of isotype switching. It is perhaps surprising that, despite being a robust and unusual clinical observation, this phenomenon, until recently, has been little studied. Recent data are supportive of this phenomenon representing aberrant B-cell activation [5].

Gender distribution of disease

PBC is a disease predominantly, but not exclusively, affecting women. Pathogenetic models for PBC must explain this predominance while not invoking processes where female gender is obligatory (for example pregnancy).

Heritability and disease associations

PBC, and the disease-independent presence of antimitochondrial antibody (AMA), occurs more frequently in close relatives of patients who have PBC than in controls, and is associated with an increased incidence of autoimmune disease of other types (most particularly in non-organ–specific autoimmune disease) in patients who have PBC and their first-degree relatives [6–8]. These observations and the finding that PBC exhibits
a higher concordance rate in monozygotic than dizygotic twin pairs point to a genetic component to disease susceptibility and suggest that this is expressed through genes that regulate the immune response [9]. Many of the familial risk/genetic studies of PBC have failed to distinguish, however, between true genetic risk and shared environmental exposure.

**Patient age**

Patients who have PBC typically present over age 40, an observation compatible with a significant, additional, acquired component to disease pathogenesis that is encountered in adult life, is cumulative in nature with threshold levels not achieved until adult life, or is so slow in its effects that the phenotype of disease is achieved only in adult life.

**Disease recurrence post transplant**

Recurrence of PBC can occur after liver transplantation [10]. There seems to be no association between degree of HLA matching between donor and recipient (donors and recipients normally are not matched for HLA in liver transplantation, resulting in a random degree of coincidental matching in transplant populations) and risk for disease recurrence [10]. This argues that the disease, at least in its recurrent form, cannot be caused by a process that is directly HLA restricted.

**Tissue tropism of disease**

PBC principally is a disease of the small intrahepatic bile ducts, with loss of the biliary epithelial cells (BEC) lining these ducts underpinning much of the subsequent cholestatic damage. PBC, however, is not restricted to the liver as abnormality of salivary and lachrymal glands (with associated cell phenotypic change similar to that seen in BEC) also occurs [11].

**Primary biliary cirrhosis as an autoimmune disease?**

PBC is associated with the almost universal development, and typically high level, of autoreactive immune responses [12]. The key outstanding issues regarding PBC as a putative autoimmune disease are the mechanism responsible for breakdown of tolerance to what are all highly conserved self-antigens and the nature of the role played by these responses (if any) in the development of target cell damage. The best characterized and most prevalent autoantibodies are directed against the 2-oxo-acid dehydrogenase family of multienzyme complexes (2-OADC) located on the inner mitochondrial membrane, all of which play key roles in energy homeostasis within the cell [13]. The predominant response is directed at the E2 and E3 binding protein (E3BP) components of pyruvate dehydrogenase complex (PDC). Antibodies
<table>
<thead>
<tr>
<th>Clinical observation</th>
<th>Reconcilable aspects</th>
<th>Non-reconcilable/unknown aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibody presence</td>
<td>(a) Clear link to autoimmunity</td>
<td>(a) Development of AMA in non-PBC infectious disease settings in the apparent absence of disease development</td>
</tr>
<tr>
<td></td>
<td>(b) High titer suggests dominant effect</td>
<td>(b) Lack of disease development in animals undergoing AMA passive transfer and induced to express AMA</td>
</tr>
<tr>
<td></td>
<td>(c) Emerging data regarding intracellular actions</td>
<td>(c) Autoantibody negative PBC is well described</td>
</tr>
<tr>
<td></td>
<td>(d) Potential interaction with surface PDC resulting in ADCC</td>
<td></td>
</tr>
<tr>
<td>Elevated IgM</td>
<td>(a) Clear link to abnormality in B-cell biology</td>
<td>(a) High degree of isotype switching of the AMA response seen in most patients</td>
</tr>
<tr>
<td></td>
<td>(b) Apparent role for TLR ligands (able to up-regulate antigen presentation in stimulating polyclonal IgM response)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(c) High IgM component of the anti-LA immune response seen in very early disease</td>
<td></td>
</tr>
<tr>
<td>Gender distribution</td>
<td>(a) Female predominance common in autoimmunity</td>
<td>(a) Effect more marked than for other autoimmune disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Mechanism unknown</td>
</tr>
<tr>
<td>Heritability and disease associations</td>
<td>(a) Familial risk a characteristic feature of autoimmune disease</td>
<td>(a) HLA association weaker than for other autoimmune diseases</td>
</tr>
<tr>
<td></td>
<td>(b) Increased personal and familial risk of autoimmunity a feature of autoimmune disease</td>
<td>(b) Most studies fail to distinguish between genetic risk and shared environmental risk (ie, families sharing space) in terms of heritability of PBC</td>
</tr>
<tr>
<td>Patient age</td>
<td>(a) Older age range than typical could represent exposure to disease trigger at later age or cumulative exposure to a rarer but retained factor until a “trigger” level of exposure is attained</td>
<td>(a) Age range atypical for autoimmune disease</td>
</tr>
<tr>
<td></td>
<td>(b) Older age range could reflect role for sex hormone triggering (eg, pregnancy or menopause)</td>
<td></td>
</tr>
<tr>
<td>Post-transplant disease recurrence</td>
<td>(a) Autoantibody remains post transplant suggesting ongoing process</td>
<td>(a) Recurrence across HLA boundaries argues against HLA-restricted T-cell responses causing recurrent disease</td>
</tr>
</tbody>
</table>

(continued on next page)
directed at PDC inhibit the function of the complex in vitro [14]. The mechanistic basis of this inhibitory effect and the apparent cross-reactivity of the antibody responses between PDC-E2 and PDC-E3BP [15] was determined with the observation that a lipoic acid (LA) cofactor, attached to PDC-E2, E3BP, and the other 2-OADC-E2 components within the inner mitochondrial space, represents a key shared component of the B-cell autoepitope within all these enzymes [15–17]; antibodies reactive with free LA are postulated as representing the original immune motif of PBC, with reactivity against LA-containing proteins, such as PDC-E2 and E3BP, arising as a result of secondary epitope spreading [18].

More recently, CD4+ T-cells directed against PDC-E2 were found to be present in the peripheral repertoire in patients who have PBC but not normal controls [19–21] and enriched within the liver, suggesting localized recruitment [21]. Liver-enriched CD8+ cells reactive with PDC-E2 also are described, again uniquely in patients who have PBC, and demonstrated to exhibit cytotoxic capability against PDC-E2-pulsed target cells [22]. The HLA class I– and class II–restricted epitopes within PDC-E2 are described in PBC, and both span the key LA-binding residue [19,23].

Although the nature of the autoreactive immune responses directed against PDC and related complexes is described in some detail, the role played by each component, if any, in disease pathogenesis remains unclear. With regard to the anti-PDC antibody response, there is no substantive evidence to suggest a mechanistic link to disease development, anti-PDC antibody development being seen in several infectious inflammatory disease settings in the apparent absence of liver disease development. Furthermore, passive transfer of mouse anti-PDC into naïve recipient mice is not associated with the development of liver pathology [24]. These findings do not, however, exclude a role for antibody in disease pathogenesis if an additional co-factor process is required in order for the effect to be observed. For example, antibody-directed cell cytotoxicity (ADCC) would not be observed in such human and animal disease settings if aberrant antigen expression on the target cells were necessary for the pathologic effect to be observed. This potentially is highly relevant given the observation that BEC from...
patients who have PBC show surface up-regulation of PDC-E2 [25]. Up-regulation of surface PDC is not, in isolation, however, sufficient to cause disease [26]. Furthermore, the conclusion that antibody does not play a direct role in disease pathogenesis only relates to conventional paradigms for antibody-mediated cell damage. It is postulated, for example, that a specific pathogenetic role for AMA may be restricted to certain isotypes of the antibody, with particular focus on dimeric IgA, which has, in humans at least,
the property of undergoing transcytosis across BEC as part of the normal secretion pathway. Dimeric IgA anti-PDC can be identified in bile [27]. Antibody penetration into mitochondria, were it to occur, reasonably might be expected to block PDC enzymatic function and to exert significant metabolic effects on the cell, including, potentially, the induction of apoptosis. In terms of underpinning clinical observations, an antibody-mediated pathogenetic effect has the conceptual advantage of explaining disease recurrence after transplant, given the near universal observation of ongoing AMA presence in post-transplant patients who have PBC. Direct antibody-mediated effects cannot explain the development of PBC in autoantibody-negative disease.

There also are data supportive of a causal role for autoreactive T-cell responses directed in the pathogenesis of PBC. The kinetics of the HLA class I–restricted PDC-E2 specific response to PDC-E2 (precursor frequency is greatest in early disease when BEC damage is peaking) are compatible with an effector response [22]. Moreover, in animal models of disease, the induction of autoreactive T-cell responses against PDC-E2 seemingly is associated with the development of PBC-like bile duct damage in spontaneous and induced models of the disease [28–35]. Histologic study of liver tissue from patients who have PBC also is supportive given the presence of
a significant T-cell–rich portal tract infiltrate around effected bile ducts and the evidence for, at some stages of the disease at least, apoptosis of BEC as a mechanism for cell “loss” (vide infra). Observations from human patients who have PBC (in whom regulatory T-cell deficiency is reported) and a series of recently described genetically modified mice that spontaneously developed both histologic features suggestive of PBC and, in some cases, AMA (and that share the characteristic of disturbed T-cell regulation) point to impairment of T-cell regulation as a potentially key element in the pathogenesis of PBC and related disorders [31–34,36].

Key clinical observations remain difficult to reconcile, however, with an autoreactive T-cell model. There is broad acceptance that response to corticosteroid therapy is limited in PBC. Significantly greater response might be predicted if T-cell autoreactivity were a key component of disease pathogenesis. Furthermore, the observation that disease recurrence can occur across HLA boundaries post transplant (in patients who typically are receiving immunosuppressive therapies with a significant T-cell directed component) also is difficult to reconcile with an HLA-restricted T-cell response a key component in the pathogenetic process.

Also critical to the PDC-directed autoimmune response model for the pathogenesis of PBC is the question of how immune self-tolerance breaks down to PDC, an enzyme expressed in all nucleated cells in the body, and which, through its fundamental role in metabolism, plays a critical role in cell survival and function. Several themes are starting to emerge regarding the unique structural properties of PDC and the role that these properties may play in rendering it immunogenic. One theme is the importance of the complex, and highly conserved, quaternary structure of PDC and its fellow 2-OADC complexes (essential for enzymatic function) and the role that this may play in allowing induction of B-cell responses that are cross-reactive between PDCs from different species. A simple model for the pathogenesis of PBC, therefore, is induction of an immune response against microbial PDC, which subsequently is cross-reactive with self. The higher affinity of the response to PDC of human compared with bacterial origin and the accompanying hierarchy of enzyme inhibitory capacity [37], however, argue against this simple model. Furthermore, there is the conceptual problem of why, given the universal presence of PDC in all commensal and pathogenic bacteria (and toll-like receptor [TLR] ligands able to activate antigen-presenting cells), the induction of PBC is not universal. Finally, and potentially critically, cross-reactivity between PDCs of different species is restricted to the B-cell compartment with even T-cell responses directed at other mammalian PDC forms (which show the highest sequence homology with human PDC) not directly associated with induction of T-cell autoreactivity [28].

A recent, and potentially exciting, possible explanation for the mechanism of breakdown of immune tolerance to PDC and its restricted expression has come with the observation that LA itself plays a fundamental role in the immunogenicity of PDC [18], and the finding that xenobiotics
showing structural homology with LA can play a significant role in triggering lipoate-directed immunoreactivity [35,38]. Several strands of data support this emerging xenobiotic model. First, higher affinity is reported to some synthetic molecules containing xenobiotic LA homologs than to LA itself; a finding compatible with the initial immune response directed at xenobiotics with subsequent cross-reactivity with LA [38]. Second, sensitization of experimental animals with constructs containing xenobiotics with structural homology to LA is associated with the development of autoreactive immune responses (at the T-cell and the B-cell levels) against native LA-containing autoantigens and, potentially crucially, the development of PBC-like liver lesions [35]. Finally, one of the key xenobiotics demonstrated as showing immune cross-reactivity with LA and able to induce autoreactivity to PDC in experimental animals with the associated development of PBC-like histologic lesions (6-bromohexanoic acid) recently has been demonstrated to compete effectively with (and under the appropriate energetic conditions out-compete) LA in terms of incorporation into PDC-E2 via the enzymes of the physiologic exogenous lipoylation pathway [39]. This gives rise to the possibility that xenobiotics present in the environment (6-bromohexanoic acid is an industrial substrate) that are immunologically cross-reactive with LA can undergo incorporation into PDC-E2, potentially rendering the whole complex immunogenic despite the protein backbone being fully self-origin. It is possible to conceive of an environmental contaminant accumulation model in which progressive incorporation of long-lasting halogenated xenobiotics over time results in eventual attainment of a threshold level that is immunologically significant in terms of generating sufficient “altered-self” PDC-E2 to trigger, under the appropriate costimulatory environment, autoreactive immune responses. This model fits with epidemiologic data suggesting that PBC has a specific geographic distribution, which is associated with potential environmental contamination (in terms of previous heavy industrial contamination or exposure to toxic waste) [40,41].

Studies addressing the issue of PDC tolerance breakdown in animal experimental models have pointed to an apparent hierarchy of tolerance maintenance as a key factor explaining the balance between PDC-directed autoreactivity and autoimmunity in PBC. The induction of breakdown of B-cell tolerance to PDC seems relatively easy to achieve, probably reflecting the high degree of conservation of the quaternary structure of the complex [29]. The induction of breakdown of T-cell tolerance to PDC is significantly more difficult to achieve, however; an observation compatible with this is the key threshold step for disease pathogenesis [29]. There are emerging data to suggest that one of the key mechanisms in the translation of breakdown of B-cell tolerance to self-PDC into T-cell tolerance breakdown is the capacity of activated B-cells to function as antigen-presenting cells, potentially able to present cross-reactive self-PDC “concentrated” through antigen-specific uptake by “nonself”-specific, but “self”-reactive, surface Ig. This possibility is strongly suggested by the observation that transfer
of activated B cells isolated from donor animals sensitized with non-self-PDC (but not PDC-naive donor animals) and pulsed ex vivo with self-PDC is sufficient to induce T-cell tolerance breakdown to self-PDC in naive recipient mice [24]. These observations raise the possibility that the B-cell response to PDC seen in PBC plays, in addition to any role related to release of pathogenetic antibody, a key “upstream” role in terms of mediating T-cell tolerance breakdown to self-PDC through augmented antigen presentation.

Further complexity to the immune model for PBC pathogenesis is suggested by emerging data—that dysregulation of the innate immune system also is a feature of the disease, potentially unmasking T-cell autoreactivity through altered APC function or down-regulation of regulatory T-cell function [42]. Peripheral blood mononuclear cells from patients who have PBC seem to have an increased sensitivity to TLR ligands suggesting chronic activation of innate immunity [5,43]. Particular attention has focused on the role played by TLR9 in B-cell activation (potentially a key activation factor for B-cell antigen presentation) as a potential explanation for polyclonal IgM production, one of the key clinical observations in PBC [5,44]. A potential in vivo mechanism for chronic TLR stimulation in PBC comes with the longstanding observation of the presence of bacterial cell wall components within the liver in patients who have PBC [45].

Although much of the work performed on the potential immune pathogenesis of PBC relates to the mitochondrial antigens, other nuclear-encoded antigens also are identified as providing reactivity in this disease and are important as markers and prognostic features in the disease. The nuclear antigens are described in detail by Muratori and colleagues elsewhere in this issue.

Primary biliary cirrhosis as an infectious disease?

The concept that PBC might have an infectious etiology dates back many years, starting with the observation of granulomatous change within the liver. More recently, the focus has been on a postulated retroviral etiology. One clinical observation above all is supportive of an infectious etiology—that of rapid recurrence of the disease after liver transplantation. Further supporting evidence that argues for an infectious etiology comes from the data relating to BEC (and salivary epithelial cell) surface expression of PDC (or a cross-reacting antigen), which is a phenomenon unique to PBC [25] (in AMA-positive and AMA-negative PBC). This phenomenon, which also recurs early after liver transplantation, can be induced in cultured BEC from normal individuals when cocultured with tissue extracts from patients who have PBC [46]. Moreover, further supernatant passage from such cultures results in, once again, induction of surface PDC expression in naive normal BEC cultures; observations interpreted as representing transmission of an infectious agent inducing up-regulation of PDC. This model was given
further stimulus by the identification of a beta-retroviral entity within culture supernatants in the passage system (described previously), and isolated from tissues from some (but not all) patients who have PBC [47]. This beta-retrovirus has significant sequence homology with mouse mammary tumor virus (MMTV), a widely used laboratory reagent [48]. These observations are provocative but remain unconfirmed; the Selmi group were unable, in parallel experiments, to replicate several of the key findings [49].

Although recent interest in terms of an infectious etiology for PBC has focused on the potential retroviral cause, there is an older literature that has linked bacterial infection with the induction of features of PBC. Potentially relevant observations include, in particular, the induction of AMA in patients who have mycobacterial and *Escherichia coli* infection (particularly in the context of chronic urinary tract infection) [50,51]. These observations make the point that infectious agents with their capacity to trigger cross-reactive immune responses (and to provide the TLR ligands that apparently are critical for antigen-presenting cell activation in PBC) remain a potentially important source of possible disease triggers. The infectious etiology and the autoimmune etiology models for PBC pathogenesis, therefore, are inextricably linked.

**Primary biliary cirrhosis as a cytopathic disease?**

Ultimately, any model for PBC pathogenesis must be able to explain BEC loss and the development of progressive ductopenia. Initial observations identified the presence of apoptotic BEC in PBC liver [52–54], an observation believed compatible, in particular, with an autoimmune etiology given the capacity for cytotoxic T cells to induce target cell apoptosis [22] and the presence of markers of T-cell cytotoxic functionality within the inflammatory infiltrates seen in PBC liver [55]. Apoptosis can occur, however, as a direct consequence of the effects of hydrophobic bile salts known to be retained within the liver in PBC [56,57]. BEC apoptosis seen after ductopenia resulting from another mechanism, therefore, could represent a consequence of early-stage PBC rather than a direct cause. This possibility is supported by the limited observations made in very early stage disease (when cytotoxic T-cell numbers are at their height within the portal tract infiltrates) [22], which suggest that BEC apoptosis is limited in its extent [58,59]. These observations all suggest that, although BEC apoptosis undoubtedly plays an important role in the pathogenesis of PBC, the nature of that role seems more complex than previously believed. This has given rise to the concept that BEC damage, rather than representing the consequence of a single mechanism, may result from a complex series of processes potentially occurring at different stages in the disease process [3].

In addition to apoptosis there are emerging data to suggest that BEC loss can occur as a direct consequence of cellular senescence, potentially compounded by the effects of oxidative stress [3,60]. The BEC changes seen in
PBC liver are associated closely with myeloperoxidase-positive macrophages present within portal tract infiltrates suggesting a potential role for chronic inflammation in oxidative stress–driven or –augmented BEC senescence. The evidence suggesting that senescence driven or augmented by oxidative stress contributes to the eventual phenotype of BEC loss gives rise to concepts of senescence acting as a mechanism for ab initio bile duct loss (where, for example, oxidative stress predominates). These data would also support a mechanism for consequential BEC loss as a result of epithelial “exhaustion” as proliferative homeostatic responses to BEC loss by other mechanisms fail, resulting in loss of the compensatory capacity, potentially regulated by the hedgehog pathway, which seems critical for the normal homeostatic response to BEC damage [3,61].

Observations in animal models of biliary obstruction and, more recently, in PBC itself, have suggested a further potential mechanism for BEC “loss,” that of epithelial to mesenchymal transition (EMT), a process in which epithelial cells undergo phenotypic reprogramming, losing epithelial markers and properties and gaining features more typical of fibroblasts [62–68]. Phenotypic studies demonstrate an intermediate stage in which epithelial and mesenchymal markers are expressed, with eventual acquisition of a full mesenchymal functional and surface expression phenotype. This model is highly attractive as an explanation for “loss” of BEC and their replacement by fibroblasts. Studies using cultured BEC have demonstrated that EMT can be induced by transforming growth factor-beta (TGF-β). A role for TGF-β in the induction of EMT in vivo is suggested strongly by the presence in BEC of features of the TGF-β signaling pathway (nuclear pSMAD 2/3 expression) [68]. Potentially important in terms of the development of novel approaches to therapy, BEC EMT driven by TGF-β in culture is reversible by antagonism of the TGF-β effect through, for example, the use of hepatocyte growth factor (HGF). Furthermore, HGF reverses liver fibrosis secondary to bile duct ligation and ameliorates PBC-like bile duct lesions in chronic graft-versus-host disease [64,69], suggesting potential in vivo therapeutic efficacy. HGF itself is expressed by BEC in affected bile ducts in PBC, suggesting that endogenous HGF production by BEC may represent a homeostatic response by BEC to EMT-inducing stimuli [63,70].

The identified mechanisms of BEC loss in PBC are not mutually exclusive. It is conceivable that all of these processes play key roles in different stages of the disease course. In one potential model, EMT could be occurring as an early process responsible for an initial ductopenic effect (an observation compatible with post-transplant recurrence observation) [67], with apoptosis occurring as an intermediate effect through the combined actions of hydrophobic bile salts and a cytotoxic T-cell response and senescence occurring as a late blow, as the homeostatic response of the BEC of regeneration through proliferation fails due to cellular exhaustion. The possibility that apoptosis may represent, in part at least, a secondary phenomenon in
PBC, taken together with the altered antigen-expression patterns associated with apoptosis (mitochondrial autoantigens implicated in PBC pathogenesis are cleaved by key apoptotic cascade enzymes [71], potentially generating “altered-self” forms of PDC, which may be immunogenic) and the fact that BEC normally express specific phenotypic features suggestive of apoptosis resistance (which are lost in PBC), which alter the cleavage properties of PDC [72], gives rise to the challenging concept that autoreactivity in PBC may occur as a consequence of initial bile duct damage rather than representing its cause. In this model, autoreactive immune responses in PBC represent an epiphenomenon occurring in the disease or a “booster” secondary damage process. This model could go some way to explain the apparent lack of response to immunomodulatory therapy in PBC. An alternative potential explanation for the apparent presence of EMT in the earliest stages of the disease process is that this process and the counter-balancing capacity, demonstrated in vitro, of the cells to undergo reciprocal mesenchymal to epithelial transition represents an element of the homeostatic response to BEC damage, rather than the mechanism of damage per se, increasing the proliferative capacity of BEC in response to insult by cycling them through a mesenchymal phase, where such capacity is increased greatly compared with the epithelial phase, before reverting to the epithelial phenotype. This concept fits well with emerging ideas suggesting that the interactions of the cell types implicated in liver injury and repair are substantially more complex than previously believed, that they reflect both sides of the balance of damage and repair (the ductular reaction, for example, representing an epithelial restorative and a pro-fibrogenic response) [61], and that they need to be viewed in a systematic way (“tissue biology” as opposed to “cell biology”) [73,74].

Summary

There is a wealth of clinical and experimental data now linked to understanding the pathogenesis of PBC. The balance of the available data strongly supports an autoimmune model. Inconsistencies within this model, however, must be acknowledged. Paradoxic observations (in particular the unusual response pattern to immunomodulatory therapies and the recurrence of disease after transplantation across HLA boundaries) need to be explained to reconcile this model. The concept of an infectious etiology is controversial but the possibility that infection acts as a trigger to disease renders the infection hypothesis fully compatible with a principally autoimmune mechanism for disease pathogenesis. Although there is little evidence that PBC represents a disease in which cytopathic processes occur as the primary effect, BEC, rather than acting as passive victims in the process, are active participants and, in all probability, ductopenia represents as much a failure of BEC to be able to respond normally to insult as a direct
consequence of that insult. It may be, therefore, that all of the autoimmune, infectious, and cytopathic pathogenetic models are “correct.”

Where does this leave us, therefore, with regard to therapy? Understanding the antigen specificity of B-cells and auto reactive T-cell responses in PBC has not influenced therapy directly (and is unlikely to so in the future). Approaches aimed at tolerizing autoreactive immune responses to PDC have proved, perhaps unsurprisingly, ineffective in terms of liver injury. PBC joins, therefore, the long list of autoimmune diseases where the naïve model of increased understanding of antigen specificity followed directly by the development of novel approaches to therapy has led to disappointment. It may be, however, that the goal of developing novel approaches to treatment of this disease will be realized by studying not the intermediate process in the disease (probably autoreactive immune responses) but the earliest stages of the disease when initial insult occurs and, in particular, the stages of BEC damage. PBC is a disease in which BEC are damaged and lost and perhaps the focus in terms of therapy should be directed precisely at this most critical process.

References


