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Webb, Gwilym J; Hirschfield, Gideon M

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PRIMARY BILIARY CHOLANGITIS IN 2016

High-definition PBC: biology, models and therapeutic advances

Gwilym J. Webb and Gideon M. Hirschfield *

In 2016, obeticholic acid — a semisynthetic bile acid analogue — became the first new licensed therapy for patients with primary biliary cholangitis in over 20 years. This therapeutic came at a time of clarity over risk stratification and paralleled by better disease understanding through biliary and immunologic mechanistic insights.

Key advances

Patients with PBC are now the beneficiaries of stratified medicine which has aided clinical and research practice.

Manipulation of the IFN γ pathway in mice led to an animal model of autoimmune cholangitis that recapitulates the female preponderance of primary biliary cholangitis (PBC)³

Bile-salt-induced apoptosis is regulated by soluble adenylyl cyclase; dysregulation of anion exchanger 2 function sensitizes biliary epithelial cells to apoptosis by activating soluble adenylyl cyclase⁵

Glycohenodeoxycholic acid reduces expression of anion exchanger 2 in biliary epithelial cells, inducing reactive oxygen species and enhancing epithelial cell senescence⁶

A clinical trial supports the efficacy of obeticholic acid in the treatment of patients failing current care¹⁰, leading to a licensed therapeutic that is predicted to change the clinical course of PBC

Primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis) is an important but rare chronic immune-mediated liver disease. Currently, 1 in 1,000 women are estimated to live with PBC, with risks of disease progression to cirrhosis and liver failure, as well as symptoms associated with the disease (particularly pruritus and an association with fatigue)⁽¹⁾. In 2016, our understanding of PBC pathogenesis has continued to be further refined on the basis of elegant basic and clinical science, including the concept of high and low risk disease, particularly as recognized after evaluation of treatment response to the first line agent ursodeoxycholic acid⁽²⁾.

Increasingly, it is recognized that a multistep model of PBC pathogenesis can be identified (Fig. 1) that encompasses: a genetic risk for autoimmunity; environmental factors that might trigger a loss of immune tolerance and/or damage biliary epithelial cell integrity; biliary epithelial injury that subsequently alters bicarbonate production and jeopardizes normal barrier functions and apoptosis; a cycle of biliary epithelial response to injury that includes apoptosis, senescence and recruitment of inflammatory cells; ongoing ductopenia and added cholestasis; and ultimately, progressive liver fibrosis and cirrhosis⁽¹⁾. In this setting, therapies for those stratified at high-risk of disease progression, despite ursodeoxycholic acid use, will be more or less effective, depending on when they are initiated and how they are delivered.

Animal models of disease have always been a struggle in PBC, as attempting to recapitulate such a complex interaction of immunologic injury and localized tissue response is inevitably challenging. Murine autoimmune cholangitis has been the subject

of many models that have spanned genetic modification, as well as xenobiotic exposure, with each model recapitulating some, but not all, features of human disease. However, work from the Gershwin and Young groups this year⁽³⁾ has made progress in developing a more meaningful disease model for study, and one that captures the gender distinction seen in PBC. This group studied mice characterized by prolonged chronic expression of IFN γ as a result of deletion of interferon 3'-untranslated region adenylate-uridylate-rich element (ARE). Interestingly, in this model, the ARE-Del^{-/-} mice developed murine PBC characterised by female predominance, upregulation of total bile acids, spontaneous production of anti-mitochondrial antibodies and portal duct inflammation. Additionally, immune-transfer experiments (CD4⁺ T-cells from ARE-Del^{-/-} mice to B6/Rag1^{-/-} mice) induced portal and parenchymal inflammation. Overall, this work highlighted the importance of interferon signalling in initial PBC pathogenesis. Inflammatory responses mediated by T helper 1 cells have been recognized as critical for loss of immunologic tolerance and this data parallels a substantial understanding of PBC genetic risk that spans key immune-regulatory pathways including IL-12 and JAK-STAT signalling⁽⁴⁾, pathways potentially additionally modifiable by estrogen exposure.

A dichotomous understanding of PBC has often been raised between the importance of immunologic injury alongside cellular response to biliary injury and cholestasis. With more sophisticated experimental approaches, over time it seems that this distinction is beginning to blur and in a way that might indicate the best therapeutic approaches for the future. Notably, it has become relevant that the Cl⁻/HCO₃⁻ exchanger (AE2; anion exchanger 2) and an intact biliary glycocalyx are important in maintaining a

biliary HCO_3^- umbrella that protects against bile acid-induced cholangiocyte damage and apoptosis. In 2016, Chang *et al.*⁽⁵⁾ explored this understanding further and demonstrated *in vitro* that soluble adenylyl cyclase, a bicarbonate sensor, regulates bile-salt-induced apoptosis in a manner dependent on intracellular Ca^{2+} stores, which are mediated by intrinsic apoptotic pathways. These findings suggest that downregulation of AE2 in PBC can sensitize cholangiocytes to apoptotic insults by activating soluble adenylyl cyclase. Intriguingly, in related work, Hisamoto *et al.*⁽⁶⁾ found that hydrophobic bile acids suppress expression of AE2 in biliary epithelial cells and this suppression induced bile duct inflammation. The hydrophobic bile acid glycochenodeoxycholic acid reduced AE2 expression in biliary epithelial cells by inducing reactive oxygen species and enhancing biliary epithelial cell senescence. Additionally, reduced AE2 expression upregulated the expression of CD40 and HLA-DR, as well as production of IL-6, IL-8 and CXCL10 from biliary epithelial cells in response to Toll-like receptor ligands (CXCL10 is secreted by several cell types in response to $\text{IFN}\gamma$). This work, therefore, equally highlights how changes to normal biliary epithelial cell physiology are relevant, not only to biliary epithelial cell response to injury, but also to subsequent signalling pathways leading to chronic inflammatory responses. The senescence-associated secretory phenotype of biliary epithelial cells might therefore be relevant in PBC and other cholestatic liver diseases, and changes in AE2 function could be a 'bridge' between the immune system (initiating and perpetuating pathways) and cholestasis. Additionally, that IL-17-positive T cells are detected in portal infiltrates close to inflamed bile ducts expressing the CCR6 ligand CCL20 is already known⁽⁷⁾. Cytokine-treated human cholangiocytes secrete CCL20 and induce CCR6-dependent migration of T helper 17 cells, suggesting that local

cholangiocyte chemokine secretion then localises these pathogenic and damaging cells to bile ducts⁽⁷⁾. Equally intriguing is that *CCL20* is a recognised genetic risk locus for PBC development, and so collectively may be a meaningful added target for intervention⁽⁴⁾.

Further advances in understanding the careful orchestration of liver injury have come from better appreciation of the gut–liver axis, with focus towards the farnesoid X receptor (FXR)–fibroblast growth factor (FGF)-19 signalling pathway. The nuclear bile acid receptor FXR is a central transcriptional sensor of bile acid metabolism and one key target gene in the gut is *FGF19*, which encodes an enterokine released into portal blood following bile acid binding to FXR. This axis is of interest because of the opportunity to augment the pathway for therapeutic benefit, with the goal of directing enhanced anti-inflammatory, anti-fibrotic and anti-cholestatic mechanisms. In the liver, FGF-19 regulates intracellular pathways that inhibit cholesterol 7 α -hydroxylase (CYP7A1), the rate limiting enzyme in bile acid synthesis⁽⁸⁾. A noncancer-promoting FGF-19 variant (M70) has been developed as a potential new therapeutic for cholestatic liver diseases, which continues to inhibit bile acid synthesis and reduce excess hepatic bile acid accumulation⁽⁸⁾. Thus, it is noteworthy that this year, in a further murine experiment by Zhou *et al.*⁽⁹⁾, modulating bile acid metabolism in a mouse model of cholangiopathy with FGF-19 and M70 rapidly and effectively reversed liver injury, decreased hepatic inflammation and reduced biliary fibrosis. These effects seemed contingent on inhibition of hepatic expression of *CYP7A1* and *CYP27A1*, genes encoding the enzymes responsible for key steps in the classic and alternate bile acid synthetic pathways. This approach is undergoing clinical trials spanning cholestatic liver disease and nonalcoholic fatty liver

disease.

Convincing human data has finally, emerged over the past 5 years supporting clinical efficacy for the semisynthetic bile-acid-derived FXR agonist, obeticholic acid, such that 2016 culminated in a new internationally approved therapy for patients with PBC. In particular, data published in 2016 from a large clinical trial with obeticholic acid⁽¹⁰⁾ added to previous clinical studies showing that FXR agonism has clear, durable effects on relevant markers of active cholestatic liver injury. Obeticholic acid reduces exposure to toxic hydrophobic bile acids by predicted and demonstrated falls in bile acid synthesis through direct and indirect (FGF-19) actions on CYP7A1-mediated bile acid synthesis, as well as bile acid excretion by hepatocytes. In conjunction with considerable academic work on surrogate markers of PBC disease course and outcome, the data from the obeticholic acid trials proved sufficient for product authorisation. Patients with PBC now have access to the first of, hopefully, many new generation treatments for their disease, which have arisen from collective ongoing efforts to finally understand PBC in high-definition.

G. Webb and G. M. Hirschfield are at the Centre for Liver Research, National Institute for Health Research Birmingham Liver Biomedical Research Unit, University of Birmingham, Wolfson Drive, Birmingham B15 2TT, UK.

Correspondence to G.M.H.

g.hirschfield@bham.ac.uk

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Competing interests statement

G.M.H. has been on primary biliary cholangitis advisory boards for GlaxoSmithKline, Intercept Pharmaceuticals and Novartis. G.M.H. has been a study investigator for CymaBay Therapeutics, Dr Falk Pharma, FF Pharma, GlaxoSmithKline, Gilead, Intercept Pharmaceuticals, NGM Bio, Novartis and Shire.

Biography

Dr Gwilym Webb is a MRC Clinician Training Fellow working at the University of Birmingham, with an interest in the development of animal models of autoimmune liver disease. He qualified in medicine from the University of Oxford.

Professor Gideon Hirschfield is Professor of Autoimmune Liver Disease at the University of Birmingham. His interest and experience is in advanced and complex liver disease management. In particular he directs autoimmune liver disease clinical care and research and has a patient practice strongly focused on integrating research into practice.

Figure 1. Converging themes in the pathophysiology and treatment of PBC

Obeticholic acid downregulates bile acid production and limits further damage to small bile ducts through an inhibitory action on the expression of the bile acid synthetic enzymes CYP7A1 and CYP27A1, and through synthesis of fibroblast growth factor (FGF)-19¹⁰. **2.** Mice with targeted disruption of MDR2 have unchaperoned bile acids, which are more reactive and cause progressive damage to biliary epithelial cells (BEC) and liver fibrosis. FGF-19 and M70 act to reduce bile acid synthesis and reduce fibrogenesis⁹. **3.** Bile acids (glycochenodeoxycholic acid) downregulate the expression of AE2 through the formation of reactive oxygen species, which has multiple downstream effects including increased expression of the effector cytokines IL-6 and IL-8, and the leukocyte chemoattractant CXCL10⁶. **4.** Through inhibition of AE2 activity and intracellular accumulation of bicarbonate, bile acids promote BEC apoptosis and make BEC more susceptible to non-bile-acid proapoptotic stimuli⁵. **5.** Dysregulated over-production of IFN γ in mice results in T-cell infiltration of periductular areas, the production of anti-mitochondrial antibody (AMA) in conjunction with B cells and the upregulation of bile acid production. The effects are more marked in female mice recapitulating the features of PBC³.

FGFR4, fibroblast growth factor receptor 4/klotho beta; FXR, farnesoid X receptor; PC, phosphatidylcholine; sAC, soluble adenylyl cyclase