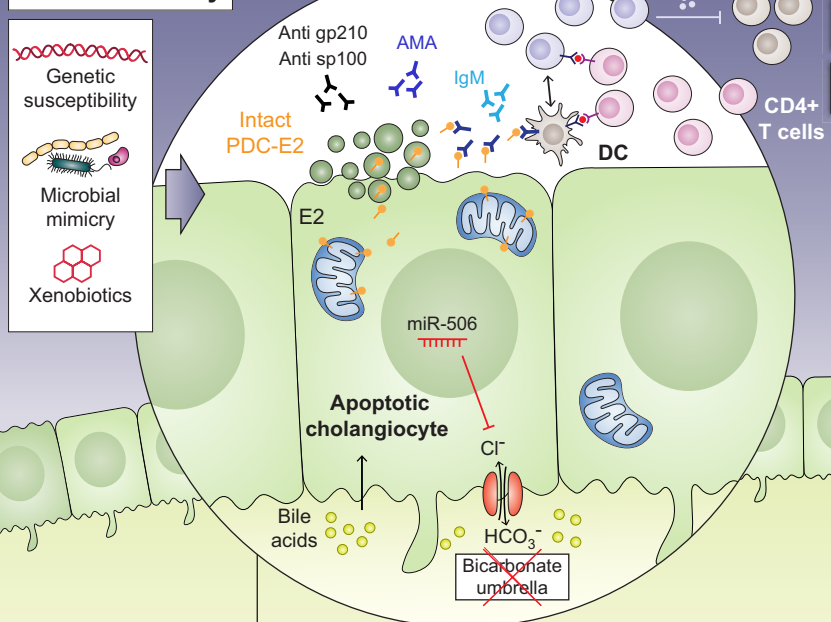


Primary biliary cholangitis: a multifaceted pathogenesis with potential therapeutic targets

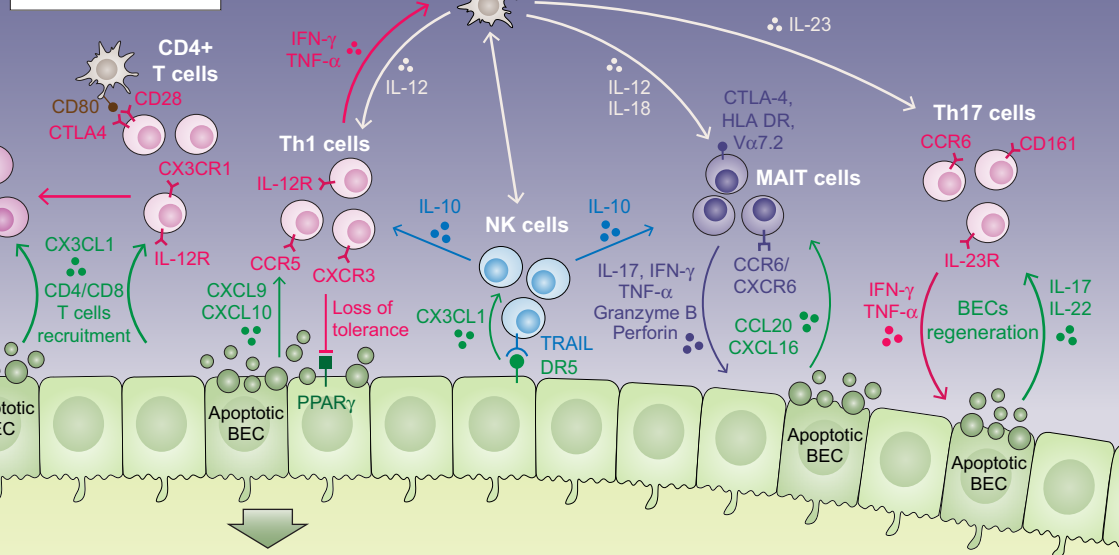
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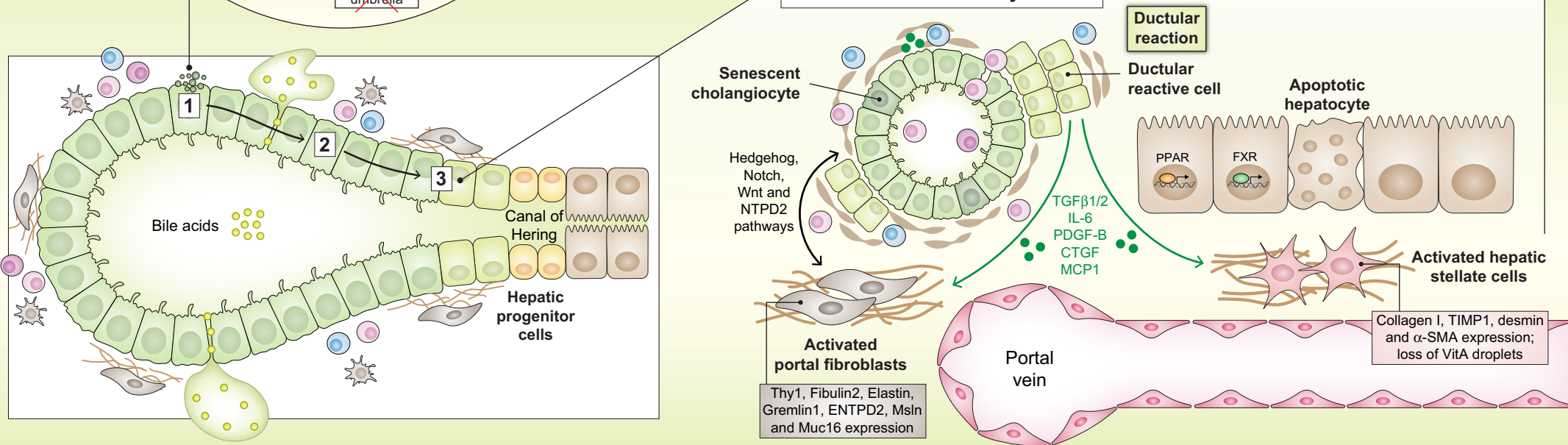
1. Autoimmunity



2. Inflammation



3. Cholestasis and biliary fibrosis



Keywords: PBC; Cholestasis; Autoimmunity; Biliary fibrosis; Biliary cirrhosis.

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Introduction

Primary biliary cholangitis (PBC) is an autoimmune liver disease characterised by destructive cholangitis affecting the small intrahepatic bile ducts, leading to chronic cholestasis and fibrosis.¹ Evidence supports the interaction of immunogenetic and environmental factors in the aetiology of PBC. An immunological attack on biliary epithelial cells (BECs) with secondary failure of biliary transporters, e.g. the anion exchange protein 2 (AE2), is traditionally considered the *primum movens*.² A recent hypothesis proposes a primary failure of BECs with the down-regulation of AE2 secondary to epigenetic mechanisms (miR-506 overexpression) which then triggers the immunological storm.³

Immunobiology

In patients with PBC, BECs are able to expose an intact and immunogenic form of pyruvate dehydrogenase complex (PDC)-E2, mitochondrial autoantigen, in apoptotic blebs.⁴ The autoreactive B cells are activated and expanded, resulting in autoantibody production. The damaged bile ducts attract naïve dendritic cells (DCs) which interact with B-cell-derived IgM to precipitate granulomatous inflammation, a typical histological feature of PBC.

The early stage of inflammation in PBC is characterised by a high level of Th1 cytokine secretion which drives the biliary damage through a direct effect and by reducing the expression of peroxisome proliferator-activated receptor- γ (PPAR- γ), an immune regulatory factor that promotes immune homeostasis.⁵

Inflamed BECs attract natural killer (NK) cells which can promote disease progression by causing BEC apoptosis. On the other hand, NK cells may inhibit adaptive immune responses through IL-10 production and induction of apoptosis in immune cells.⁵

While Th1 plays a key role in the disease onset, Th17 is necessary for disease perpetuation. The innate immune response stimulates BECs to produce Th17-inducible cytokines (e.g. IL-17).⁵ Another source of IL-17 is mucosal-associated invariant T (MAIT) cells, which are innate-like T cells constituting a significant proportion of circulating and hepatic T cells; MAIT cells can induce anti-inflammatory macrophage polarization. Repetitive IL-12 and IL-18 stimulation induces MAIT cells to evolve toward an exhausted, profibrogenic phenotype which can contribute to the development of hepatic stellate cell (HSC)-mediated liver fibrosis.⁶

Cholestasis and biliary fibrosis

In the inflamed portal tracts, chronic bile duct damage leads to bile leakage, retention of hydrophobic bile acids that cause local bile salt injury. During cholestasis, a complex system of adaptation prevents overloading of hepatocytes with bile salts. This includes downregulation of uptake transporters, upregulation of basolateral bile salt export systems, interruption of the enterohepatic circulation and bile salt absorption in the ileum and FXR-mediated production of FGF19 with significant reduction of *de novo* bile salt synthesis.⁷

Inflammation is the primer of the reparative response and biliary fibrosis in PBC. Injured BECs express a “reactive” phenotype, the ductular reactive cells (DRCs) which represent hepatic progenitor cells committed toward biliary differentiation; these cells are a hallmark of ongoing pathological repair.⁸ DRCs have the ability to produce cytokines, growth factors, and angiogenic factors, which establish powerful paracrine communications

with multiple stromal cell types, including portal fibroblasts and HSCs, inflammatory cells, Kupffer and endothelial cells. This complex of cells is called ductular reaction, which represents the pacemaker of liver fibrosis.⁸ As the disease progresses, the persistent biliary inflammation fuels a reparative reaction, with excessive deposition of fibrotic tissue in the portal space.

Therapeutic targets

Evolution in our understanding of disease mechanisms is leading to the advent of novel and re-purposed therapeutic agents targeting key processes. Biological drugs targeting the ‘upstream’ immune response have conferred dismal results so far.^{9,10} Promising results have come from specific modifiers of hepatobiliary secretory mechanisms against bile acid-mediated cytotoxicity which target the ‘downstream’ biliary and fibrotic injury, e.g. agonists of nuclear receptors (FXR and PPAR).⁷ Combination therapy targeting several pathways using a stratified approach to patient phenotype is the way forward.

Conflict of interest

Please refer to the accompanying ICMJE disclosure forms for further details.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2020.05.041>.

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