Work in Progress
Drugs in Development

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KEYWORDS

• Primary biliary cirrhosis • Unmet need • Novel therapies • Immunomodulators

KEY POINTS

- A proportion of patients with primary biliary cholangitis are unresponsive to, or intolerant of, ursodeoxycholic acid and obeticholic acid; these patients need alternative therapies.
- The recently approved obeticholic acid acts through the farnesoid X receptor. Other compounds exploiting the pathway and one of its key mediators, fibroblast growth factor 19, are under development.
- The peroxisome proliferator-activated receptors family of receptors modulate immune responses, bile acid metabolism, and fibrosis, and may have beneficial effects in primary biliary cholangitis.
- Drugs that inhibit the reabsorption of bile acids in the ileum have been shown to have marked short-term efficacy in treating pruritus.
- Immunomodulatory agents such as those blocking CD40-CD40L interactions, sphingosine-1-phosphate signaling and CX3CL-mediated leukocyte trafficking are under active investigation.

INTRODUCTION

Primary biliary cholangitis (PBC) is an uncommon chronic autoimmune disease of uncertain etiology where there is progressive destruction of small bile duct epithelial cells (**Fig. 1**).[1] The disease is closely associated with the development of autoantibodies including antimitochondrial-specific antinuclear antibodies. With time, PBC results in damage and the disappearance of small bile ducts, leading to intrahepatic

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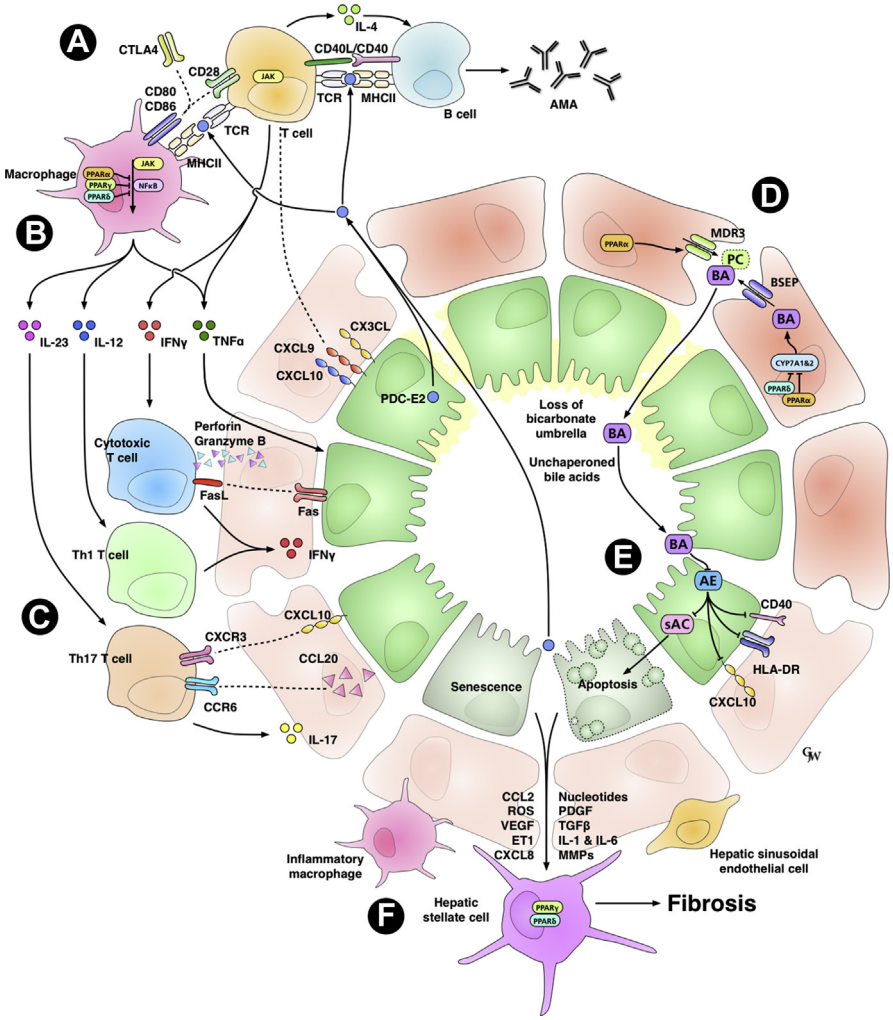

Fig. 1. Selected pathogenic mechanisms in primary biliary cholangitis. (A) Antimitochondrial antibodies are produced through interactions of T and B cells that are specific to PDC-E2. B-Cell activation is promoted by costimulatory molecules including CD40/CD40 L. T-cell activation is both through the TCR and through secondary costimulation through CD28, the latter is regulated by T-cell–expressed or exogenous CTLA4. (B) Immune cell activation is in part mediated by JAK-STAT and NF-κB signaling; PPAR ligation may reduce NF-κB activation. (C) Activated T cells (positioned by CXCL9, CXCL10 and CX3CL) produce cytokines including IFN-γ, TNF-α, and interleukin (IL)-4. With disease progression, cytotoxic and Th1 dominant inflammatory infiltrate shifts toward an increase in Th17-positive cells. Cytotoxic T cells induce apoptosis or senescence through FasL–Fas interactions and the secretion of perforins and granzyme B; both cytotoxic T cells and Th1 cells produce cytotoxic IFN-γ; IL-17–secreting Th17 cells appear later and are positioned by CXCR3–CXCL10 and CCR6-CCL20. (D) Enzymes including CYP7A1&2 convert cholesterol to BAs, which are exported by bile salt exporter pumps. BA production is reduced by ligation of FGFR4, PPAR-α or PPAR-δ. See also Fig. 2. In health, BA are chaperoned by phosphatidylcholine and exported by MDR3. (E) In primary biliary cholangitis, impaired activity of the apical AE2 and bicarbonate secretion lead to unchaperoned BA directly interfering with the BEC membrane. BEC are