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Pathogenesis of Cholestasis

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INTRODUCTION

Cholestasis liver diseases occur from failure of hepatobiliary production and excretion of bile, where bile cannot flow from the liver to the duodenum, which cause bile constituents to enter the circulation. In some conditions, serum bile salts may be markedly elevated while bilirubin is only modestly elevated and vice versa. Two obstructive types of cholestasis, first is a mechanical blockage in the duct system that can occur from a gallstone or malignancy, and second metabolic types of cholestasis which are disturbances in bile formation that can occur because of genetic defects or acquired as a side effect of many medications. The histopathologic definition of cholestasis in the appearance of bile within the elements of liver usually associated secondary hepatocellular injury.

There are numerous causes, which are identified by laboratory testing, hepatobiliary scan, and sometimes, liver biopsy and surgery, which treatment depends on cause. Many liver diseases have been demonstrated to have cholestatic pathophysiology, such as conjugated hyperbilirubinemia, jaundice cholangiocarcinoma, bile duct stone, primary biliary cirrhosis, biliary atresia, and primary sclerosing cholangitis [1].

EPIDEMIOLOGY

Cholestasis is not a primary cause of death, but it is the cause of considerable morbidity as indicated above in pathophysiology. Supersaturation of bile with cholesterol or bilirubin, gallbladder hypomotility, and an imbalance of crystallization promoters (eg, mucin) [2] that combine to promote gallstone formation, therefore the incidence of gallstones differs markedly worldwide, reaching 50% in the American Indian population, 15% to 20% in the European population, approximately 10% in the Asian population, and less so in African populations [3].

The immune-mediated biliary disorders, Primary Biliary Cirrhosis **(PBC)** and Primary Sclerosing Cholangitis **(PSC)** represent the most important small and large bile duct diseases. The incidence and prevalence rates for PSC vary from 0 to 1.3 per 100,000 inhabitants/year and 0 to 16.2 per 100,000 inhabitants, respectively, whereas the incidence and prevalence of PBC range from 0.3 to 5.8 per 100,000 inhabitants/year and 1.9 to 40.2 per 100,000 inhabitants, respectively [4-6].

PATHOGENESIS OF CHOLESTATIC LIVER DISEASE

Cholestasis can result from genetic defects, mechanical aberrations, toxins, or dysregulations in the immune system that damages the bile ducts and cause accumulation of bile and liver tissue damage which include the responses of cholangiocytes and hepatocytes to injury as named cholestatic liver disorders.

Cell Biology of Cholestasis

Secretory Function and Bile Acid Transport

Enterohepatic circulation of bile acids is fundamentally composed of two major processes: secretion from the liver and absorption from the intestine. Hereditary and acquired defects of BA transporters are involved in the pathogenesis of several hepatobiliary disorders including cholestasis, gallstones, fatty liver disease and liver cancer, but also play a role in intestinal and metabolic disorders beyond the liver. In the hepatocytes, the vectorial transport of bile acids from blood to bile is ensured by Na+ Taurocholate Co-Transporting Peptide **(NTCP)** and Organic Anion Transport Polypeptides **(OATPs)**; this transporter also mediates the hepatic uptake of many drugs [7].

After binding to a cytosolic bile acid binding protein, bile acids are secreted into the canaliculus via ATP-dependent Bile Salt Excretory Pump **(BSEP,** ABCB11) [8] and Multi Drug Resistant Proteins **(MRPs)** [9]. MRP2 and MRP3 regulate canalicular excretion of organic anions, such as bilirubin. Formation of mixed micelles in bile results from the presence of bile acids, cholesterol, and phosphatidylcholine, and the phospholipid export pump [10]. While unconjugated bile acids may passively diffuse across the small intestinal and colonic epithelia, bile acids are actively absorbed in the distal ileum via Na^+-dependent Apical Sodium Dependent Bile Acid Transporter

(ASBT). The intracellular transport of bile acids across the enterocytes is facilitated by the Ileal Bile Acid Binding Protein **(IBABP)** while them efflux through organic solute transporter α and β (OSTα/OSTβ). Bile acids re-enter the portal blood completing their enterohepatic circulation.

Bile acids synthesis and bile acid transporters are regulated through nuclear receptors and endocrine routes, including Farnesoid X Receptor **(FXR)**, Liver X Receptor **(LXR)** α/β, Peroxisome Proliferator-Activated Receptors **(PPAR)** α. In mice, dietary cholesterol induces the transcription of cholesterol 7-alpha-monooxygenase or cytochrome P450 7A1 (CYP7A1) and thereby enhances the conversion of cholesterol to bile acids through LXRα [11]. Bile acids are not simply metabolic by-products, but are essential for appropriate absorption of dietary lipids and also regulate gene transcription. Among the genes regulated by bile acids are CYP7A1, the rate-limiting enzyme in bile acid biosynthesis [12]. The transcriptional repression of CYP7A1 by bile acids is dependent on the nuclear hormone receptor FXR [13]. FXR activates transcription upon binding to bile acids and exist as an obligate heterodimer together with RXR when binding to DNA [14]. Recent study display that mutations in the nuclear bile acid receptor FXR cause progressive familial intrahepatic cholestasis [15].

Inflammatory Response

In liver structure including parenchymal cells, the hepatocytes and cholangiocytes, but also nonparenchymal cells such as Hepatic Stellate Cells **(HSCs)** and liver Sinusoidal Endothelial Cells **(LSECs)** directly act as primary sensors for and triggers of immune responses. The sinusoids contain a diversity of immunologically active cell types, including both lymphocytes and myeloid cells [16]. Under normal conditions, cytosolic bile acids in hepatocytes and cholangiocytes are kept at levels below the critical micellar concentration, but in cholestatic hepatopathies that bile acids build up inside hepatocytes and cholangiocytes. Cytotoxic bile acids can differentially induce inflammatory response, necrosis or apoptosis depending on the severity of the cholestasis [17,18]. Chronic cholestatic liver diseases encompass a range of disorders affecting the hepatobiliary system and arise secondary to a variety of causes, including molecular defects caused by genetic variation or drugs, structural changes due to congenital disorders, or autoreactive bile duct injury.

Inflammation contributes to liver injury during cholestasis, that mechanisms by which cholestasis initiate, that is bile acids act as inflammagens, and directly activate signaling pathways in hepatocytes that stimulate production of proinflammatory mediators [19]. In response to inflammation, cholangiocytes secrete cytokines and chemokines {eg, tumor necrosis factorα (TNFα), IL-1, or interferon gamma (INFγ)} that recruit and activate immune cells, including T cells, macrophages, and Natural Killer **(NK)** cells. Early study show that the IKK/NF-κB signaling pathway regulates immune and inflammatory responses and plays a critical role in protecting cells from cytokine-induced death and oxidative damage, which IKK/NF-κB signaling could be implicated in bile duct disease [20-22], and IKK signaling may be implicated in human biliary diseases.

Immunologic role

Cholangiocytes interact with members of the immune system in a number of ways, such as constitutively express and secrete chemotactic agents for neutrophils, monocytes, and T cells, including IL-8, IL-6, and Monocyte Chemotactic Protein-1 **(MCP-1)** [23]. In under basal conditions, cholangiocytes express low levels of lymphocyte adhesion molecules. However, autoimmune diseases of the liver are chronic inflammatory processes leading to injury of hepatocytes and cholangiocytes that recruit and activate immune cells, including T cells, macrophages, and Natural Killer **(NK)** cells [24]. Diverse mechanisms of these immunological processes result in PBC, PSC or Autoimmune Hepatitis **(AIH)**, but the etiology of they has still not been completely unraveled. Previous studies have suggested a critical involvement of autoreactive T cells in the pathogenesis of human PBC, and demonstrated that CD8 T cells play a critical role in the pathogenesis of PBC [25,26]. T cell reaction plays a significant role in immune-mediated cholangitis in PBC. Significantly higher level of PDC-E2-specific autoreactive CD4+ T cells and CD8+ T cells has been found in liver and regional lymph nodes as opposed to their peripheral counterparts [27]. Recent study suggested that Invariant NK **(iNK)** T cells were involved in the initiation of the original loss of tolerance in PBC, and it play complex roles in bridging innate and adaptive immunity by engaging with glycolipid antigens presented by CD1d [28].

Cholangiocytes also secrete and transport protective immunoglobulins by Immunoglobulin **(Ig)** A, which synthesized by plasma cells around bile ducts and secreted into bile after it binds to the polymeric Ig receptor located on the basolateral membranes of cholangiocytes. Therefore, IgA has a role in biliary mucosal immune defense; by preventing the attachment of pathogens or their toxins to the cholangiocytes surface, it protects biliary ducts [29].

Cell death

Intrahepatic cholestasis is associated with the accumulation of abnormally high levels of hydrophobic bile acids in the liver, which cholestasis with elevated cytotoxic effects in hepatocytes and bile duct cells, such as Deoxycholic Acid **(DCA)** are responsible for hepatocyte cell death during intrahepatic [30]. It has been proposed that cytotoxic bile acids can differentially induce either necrosis or apoptosis depending on the severity of the cholestasis; finally, bile acid toxicity can result in organ failure [31]. Early study show that hydrophobic bile-acid-induced apoptosis involves the activation of the intrinsic (mitochondrial) pathway, triggered by the release into the cytosol of pro-apoptotic mitochondrial factors through pores in the mitochondrial membranes and impairment of mitochondrial function and integrity in hepatocytes, and probably in cholangiocytes, by inhibiting the most important mitochondrial events leading to apoptosis, i.e. Mitochondria Permeability Transition **(MPT)**- and Bcl-2-associated pore formation [32].

Cell death by apoptosis is a prominent feature in a variety of liver diseases. It is likely that apoptosis is the initial cellular response to liver and biliary injury and may thus initiate several cellular and cytokine cascades. Inflammation contributes to liver injury during cholestasis, that

mechanisms by activation of Toll-like Receptor 4 **(TLR4)**, either by bacterial Lipopolysaccharide **(LPS)** or by Damage-Associated Molecular Pattern Molecules **(DAMPs)** released from dead hepatocytes, triggers an inflammatory response [19]. TLRs can recognize a virtually unlimited combination of pathogen-associated molecular patterns and DAMPs, however, the downstream signaling pathways they share are similar. Specifically, recent data suggest a direct link between upregulated apoptosis, the subsequent release of inflammatory mediators, and the development of hepatic fibrosiss [33,34]. Such an inter-relationship has also been well documented for autoimmune and cholestatic liver diseases [35]. In the injured cholestatic liver, apoptosis has long been recognized as a direct consequence of bile acid-mediated injury. It is now apparent that inflammation and necrosis play an equal or even more prevalent role [36].

Mechanistic Insights from Genetic Studies Hereditary Cholestatic Syndromes

In hereditary cholestasis syndromes, such as Progressive Familial Intrahepatic Cholestasis **(PFIC)**, mutations in bile canalicular transport are the primary cause of cholestasis, and the main clinical manifestations include pruritus and jaundice; however PFIC patients usually develop fibrosis and end-stage liver disease before adulthood [37]. The incidence of PFIC is considered to be about 1 to 2/100,000 births, which accounts for 10–15% cases of neonatal cholestasis syndrome and 10–15% of children requiring liver transplantation [37,38]. Diagnosis of PFIC is a challenging matter that involves the summation of liver histological parameters, clinical, laboratory and radiological; however specific investigations to exclude other causes of neonatal cholestasis. Mutations in four important canalicular transporter genes or bile acid synthetic pathway cause PFIC-1, PFIC-2, PFIC-3 and PFIC-4, which are autosomal recessively inherited disorders manifesting in neonates, infants, and children [39].

PFIC1 (the former Byler disease) is an autosomal recessive disease caused by mutations of the putative aminophospholipid transporter ATP8B1 (Formerly Named **FIC1**), which leads to the development of liver cirrhosis in early childhood. Mutations in the ATP8B1 function also cause loss of lipid asymmetry in canalicular membranes of hepatocyte resulting in dysfunction of BESP [40,41]. Therefore, both primary ATP8B1 and BSEP deficiencies lead to hepatocyte bile acids overload and are involved in severe as well as milder or benign phenotypes [41-44]. Recent study evaluate that liver tissue immune histochemistry of BSEP and MDR3 proteins in differentiating PFIC from other causes of neonatal cholestasis, particularly, when genotyping is unavailable [45].

PFIC1-2 was also previously known as Byler disease and is a result of by mutations of BSEP, which is the main exporter of bile acids from hepatocyte to canaliculi against a concentration gradient [46]. As a result, there is decreased biliary bile salt secretion, bile flow, and hepatic accumulation of bile acids. BSEP mutations also have been associated with Benign Recurrent Intrahepatic Cholestasis Type 2 **(BRIC2)** [47], drug-induced cholestasis [48], hormone-dependent Intrahepatic Cholestasis of Pregnancy **(ICP)**, biliary lithiasis [49] and transient neonatal cholestasis [50].

PFIC-3 is an autosomal recessive disorder of cholestasis of hepatocellular origin, which is caused by mutations of ABCB4 gene, encodes the MDR3 protein [10]. The onset of PFIC3 is typically in infancy or in childhood, but their clinical relevance in adults remains ill defined. MDR3 P-glycoprotein is a phospholipid translocator involved in biliary phospholipid excretion, which is predominantly, if not exclusively, expressed in the canalicular membrane of the hepatocyte. The exact prevalence of PFIC3 remains unknown, but the estimated incidence varies between 1/150,000 [51].

PFIC4 is caused by homozygous or compound heterozygous mutation in the Tight Junction Protein 2 **(TJP2)**, that cause failure of protein localization and disruption of tight-junction structure, leading to severe cholestatic liver disease [52]. Recent studies reported 2 patients with PFIC4 who developed Hepatocellular Carcinoma **(HCC)**. The first was a 26-month-old Caucasian female who had had intermittent jaundice of neonatal onset and normal Gamma-Glutamyl Transferase **(GGT)** and the patient died 3 weeks after admission. The second patient was a 6-month-old Caucasian male referred for persistent cholestasis with near-normal GGT after hepatoportoenterostomy for presumed biliary atresia [53]. Mutations in TJP2 resulting in progressive intrahepatic cholestasis may predispose to hepatocellular carcinoma in early childhood, warranting close monitoring and early liver transplantation [53].

ETIOLOGY OF CHOLESTASIS

Intrahepatic Cholestasis occurs inside the Liver

Intrahepatic cholestasis of pregnancy

Intrahepatic Cholestasis of Pregnancy **(ICP)**, also known as Obstetric Cholestasis **(OC)**, is a liver disease specific to pregnancy [54]; therefore, bile acids are elevated in the blood of women with ICP lead to fetal arrhythmia, fetal hypoxia and potentially fetal death in utero [55]. In Europe, ICP has been reported to affect approximately 1 in 140 United Kingdom pregnancies with a varied global incidence, and occur more commonly in winter months in some countries [56].

A number of studies have demonstrated an association between higher maternal serum bile acid levels, increased rates of fetal complications and abnormal liver function tests, in particular when serum bile acids are raised above 40 μmol/L [57,58]. In ICP maternal bile acids cross the placenta and accumulate, resulting in a reversal of the trans-placental gradient of bile acid concentration composition, whereby the primary bile acids, Taurocholic Acid **(TC)** and Taurochenodeoxycholic Acid **(TCDCA)** predominates [59]. The cause of intrahepatic cholestasis remains unclear but is related to abnormal biliary transport across the canalicular membrane [60,61]. Further details of the epidemiology (mechanism association Hepatobiliary transporters) of ICP are reviewed in [54].

UDCA is naturally-occurring tertiary bile acid, normally comprising about 3% of the human bile acid pool and the most commonly used treatment for ICP. Small studies show evidence of

maternal benefit (confirmed by a recent meta-analysis [62]) but no study has been powered to confirm a feto-protective effect of UDCA treatment. In some cases rifampicin is used as a second-line treatment [63]. For a more comprehensive review of ICP treatment see [64,65].

Primary biliary cirrhosis

Primary Biliary Cirrhosis **(PBC)** is a chronic cholestatic liver disease of autoimmune origin characterized by highly specific Antimitochondrial Antibodies **(AMAs)** that presents with chronic, progressive cholestasis, and liver failure [66,67]. PBC is characterized histologically as cholangitis of the small bile ducts (Chronic Nonsuppurative Destructive Cholangitis; **CNSDC**), eventually followed by extensive loss of small bile ducts, characteristically associated with anti-mitochondrial antibodies [68] and is present in around 1 in 1,000 women over the age of 40 [66]. Circulating AMA, leading to an immune complex of AMA-apotope, which may stimulate macrophages to secrete enormous amount of pro-inflammatory cytokines which unique apoptotic feature of Biliary Epithelial Cells **(BECs)** may contribute to apotope presentation to the immune system, causing unique tissue damage in PBC [69]. A BSEP haplotype revealed association with higher Mayo Risk Scores, suggesting a possible role in disease progression [70]. Preview study found that BSEP gene were highly associated with PBC susceptibility and explored the association between four polymorphisms of BSEP and the susceptibility of PBC in Chinese population. They suggest that BSEP gene has been attached great importance in the susceptibility of PBC and the response rate of UDCA treatment of PBC patients [71]. In early stage PBC patients with normal bile acid and bilirubin levels hepatic sarcoidosis presents a difficult diagnostic problem, new report investigated that Gd-EOB-DTPA-enhanced MRI may provide a useful detection method for liver disease in patients with LC-PBC [72].

Primary sclerosing cholangitis

Primary Sclerosing Cholangitis **(PSC)** is a chronic cholestatic liver disease, characterized by chronic inflammation and fibrosis of bile duct epithelial cells which leads to progressive cholestasis, hepatic injury, and eventually liver cirrhosis [73]. During chronic cholestatic disease, toxic bile acids accumulate and induce cholangio- and hepatocellular apoptosis by specific signaling pathways [74,75]. A potential role for a transporter defect (i.e., MDR3) in the pathogenesis of PSC has been proposed, which MDR3 defects have a unique phenotypic complexity with a wide spectrum of cholestatic syndromes spanning from the neonatal period to adulthood and provide a unique potential link between a hepatocellular transporter defect and bile duct injury, since mice lacking Mdr2 (the rodent homolog of human MDR3) develop sclerosing cholangitis macroscopically and microscopically resembling PSC in humans [76-78].

The pathogenesis of PSC is still elusive; however, both an immune-mediated injury of the bile ducts as well as increased recruitment of intestinal-primed T lymphocytes, other cell types, including NK cells, macrophages, B cells, and biliary epithelial cells to the biliary tracts seem to contribute to disease development and progression [79]. Recently report show that the G-protein-

coupled bile acid receptor 1 (as known as TGR5) promotes chloride and bicarbonate secretion, triggers cell proliferation, and prevents apoptotic cell death in biliary epithelial cells. They suggest TGR5 has a role in the pathogenesis of PSC [80].

PSC is a progressive cholestatic condition of unknown pathology which often associated with autoantibodies and closely linked to Inflammatory Bowel Disease **(IBD)**, which is found in 60–80 % of PSC patients and the possible development of neoplasms at the biliary, liver, and colon level [81]. Indeed, no therapies have been proven to improve survival or ameliorate the natural history of PSC. Liver transplantation is successful for patients with end-stage liver disease, and PSC now accounts for 5% of liver transplants done in the United States [73].

Certain Medicines can also cause Cholestasis

The liver is the importance central organ that responsible for the selective uptake, metabolism, and excretion of drugs, xenobiotic, and environmental toxins. Hepatocytes are highly polarized cells with distinct sinusoidal, lateral, and apical membrane domains. The molecular identication of transport proteins that mediate the sinusoidal uptake and biliary secretion of bile acids and other organic solutes, many of which are drugs, has greatly expanded the understanding of the cellular mechanism for bile formation and its dysregulation in cholestatic conditions, including drug induced cholestasis [82-84]. Drug-induced cholestasis is frequent among the differential diagnoses in patients with cholestasis and normal hepatobiliary imaging. The incidence and associated health care costs secondary to drug-induced cholestasis are not available, in part because most drugs commonly cause asymptomatic cholestasis associated with mild abnormalities in the serum liver profile. A Danish study of 110 cases of Drug Induced Liver Injury **(DILI)** from 1978 to 1987 reported a 17% prevalence of acute cholestatic injury [85]. A Swedish adverse drug reactions advisory committee reviewed 784 reported cases of DILI between 1970 and 2004, almost half of which had either cholestatic or mixed cholestatic hepatic toxicity [86]. Nevertheless, a wide variety of commonly used drugs can induce cholestatic liver injury including nonsteroidal anti-inflammatory drugs, antihypertensive, antidiabetics, anticonvulsants, lipid-lowering agents, and psychotropic drugs [85,87-89].

Amoxicillin/clavulanate

Amoxicillin/clavulanate is synthetic penicillin that is currently commonly used, especially for the treatment of respiratory and cutaneous infections. Recent study shows that case report of a 63-year-old male patient who developed cholestatic hepatitis after use of amoxicillin/clavulanate [90].

Chlorpromazine (CPZ)

Chlorpromazine **(CPZ)** is an antipsychotic medication that is primarily used to treat psychotic disorders such as schizophrenia. Early evidence shows that treatment with the Lipopolysaccharide **(LPS)** predisposes the liver to toxic effects of several xenobiotics including

the known Hepatotoxicants And Acetaminophen **(APAP)** and CPZ [91]. CPZ is mostly shown to induce cholestatic liver injury and caused several idiosyncratic responses during its therapeutic use [92,93].

Terbinafine

Terbinafine is a widely prescribed antifungal medication for onychomycosis, which appears to produce mixed hepatocellular-cholestatic injury [94]. The precise mechanism of injury with terbinafine is not entirely clear, but interference with bile flow by canalicular injury or other lesions of bile secretion provoked by idiosyncratic reaction is presumed to play a major role [95,96].

THERAPY OF CHOLESTATIC LIVER DISEASE

Cholestatic liver disease is the consequence of many hepatobiliary injuries, which variety of pathways contribute to liver tissue damage; therefore, new therapies might be developed to target pathways that mediate these processes. UDCA is currently the most widely used therapeutic agent for the treatment of hepatopathies of a cholestatic nature, and the only one approved by U.S. FDA (Food and Drug Administration) to treat PBC [97]. UDCA protects cholangiocytes against toxicity exerted by hydrophobic bile acids, stimulates hepatobiliary secretion, and inhibits bile acid-induced apoptosis in hepatocytes [98]. A combined analysis of three large clinical trials has demonstrated that the use of UDCA in PBC is safe, improves serum liver biochemistries and significantly prolongs free survival [99]. Although the efficacy of UDCA is debated, it is largely accepted for most patients with PBC and obstetric cholestasis, whereas the effects of UDCA in patients with PSC are limited [67, 100, 101]. New therapies for PBS, is Obeticholic Acid **(OCA)** also known as INT-747 that is a natural ligand for FXR. OCA has been tested in phase II and III international trial suggest that it may be effective in achieving a biochemical response in approximately 40 % of patients who do not completely respond to UDCA [102]. In addition, both UDCA and OCA increase the presence of bile acid transport proteins, including the MRP3 and BSEP, on the canalicular membrane and have anti-apoptotic effects [103]. On the other hand, biologic agent including anti-CDC20 [104, 105], anti-IL12 [106] and AV1142742 (Rhudex) [107] that are targeting and other proteins with important roles in modulating inflammation and immune response have revolutionized the treatment of a number of autoimmune diseases, but have been studied in a limited fashion in PBC.

Intractable itching is a symptom of cholestatic liver disease of various causes that is bothersome and difficult to manage, that given the debilitating consequences of pruritus, symptomatic treatment is frequently necessary. There are many medications including cholestyramine, rifampin, opioid antagonists (i.e., naloxone, naltrexone), phenobarbital, and antihistamines have been used to treat cholestatic-induced pruritus, none has resulted in uniform success [108].

CONCLUSIONS

Cholestasis liver disease is the consequence of hepatocytes, hepatobiliary and hepatocellular transporters insults that cause bile acids disorder, cell apoptosis, inflammatory and immune responses. However, pathogenesis of cholestatic liver disease is varieties of pathways contribute to liver tissue damage and the reparative response, so there has been no effective treatment for the advent of drugs. The most common and most effective clinical treatment of UDCA; on the other hand, OCA has been tested in phase III international trial suggest that it may be effective in cholestasis liver disease. UDCA and OCA are mediate bile acids and transporter protein-associate target pathways. In conclusion, there remain cholestasis-associate patients with an incomplete response to UDCA and remain at risk for disease progression, therefore modulating bile acid physiology and targeting specific immune responses is an important approach to developed new therapies.

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