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The role of inflammation in cholestasis – clinical and basic aspects

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Abstract

Hepatobiliary transport systems are essential for the uptake and excretion of a variety of compounds including bile acids. Disruption and dysregulation of this excretory pathway results in cholestasis, leading to the intrahepatic accumulation of bile acids and other toxic compounds with progression of liver pathology. Cholestasis induced by inflammation is a common complication in patients with extrahepatic infections or inflammatory processes, generally referred to as sepsis-associated cholestasis. Microbial products, including endotoxin, induce signaling pathways within hepatocytes either directly, or through activation of pro-inflammatory cytokines, leading to rapid and profound reductions in bile flow. The expression and function of key hepatobiliary transporters are suppressed in response to inflammatory signaling. These pro-inflammatory signaling cascades lead to repressed expression and activity of a large number of nuclear transcriptional regulators, many of which are essential for maintenance of hepatobiliary transporter gene expression. Interestingly, recently discovered molecular crosstalk between bile acid activated nuclear receptors and pro-inflammatory nuclear mediators may provide new means of understanding adaptive processes within liver. All together, inflammation-induced cholestasis, and the effects of retained molecules in cholestasis on inflammatory signals, are interwoven in the liver, providing potential opportunities for research and therapeutics.

Keywords

Liver; cholestasis; inflammation; transporters; bile acids

Basic aspects of inflammation in cholestasis

Bile formation is normally mediated and maintained by the coordinated function of a set of membrane transporters located within membranes of hepatocytes, cholangiocytes and enterocytes. These transporters work together to import and secrete the various molecules that comprise bile, also allowing for processing of some of these components via intracellular enzymes and signaling molecules (see accompanying articles in this issue for details on the transporters and nuclear receptors that regulate bile formation, as well as roles in human disease [1–7]). The flux of, bile acids, the main solute in bile, drives the majority of bile formation, while impairments of bile acid dependent and bile acid independent fractions of bile flow bring about cholestasis (see these recent reviews for details [8–16]). In essence, how well these hepatobiliary transporters function relates directly to the amount and composition of bile. Function of these transporters is regulated at multiple levels, from initiation of RNA transcription in the nucleus to microdomain localization in the membrane.

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In the nucleus, transcription is regulated by a host of factors that involves members of the nuclear receptor superfamily, as well as other key regulators of the transcription complex [17,18]. After RNA synthesis and translation, the functioning and proper localization of hepatobiliary transporter proteins depends upon intact intracellular transport pathways and the cytoskeleton, as well as signaling regulators that posttranscriptionally modify protein activity, localization, and stability. Given all the steps involved in maintaining the expression of the proteins that drive this important process, as well as its role in maintaining whole body homeostasis and liver health by handling potentially damaging and bioactive small molecules at high concentration, it is not surprising that the cells involved in bile flow adjust the expression and function of their key molecular components in response to injury and stressors. Such an orchestrated response is evident where the liver rapidly reduces bile formation in adaptation to infection and inflammation. Inflammation-induced cholestasis is thus one of the central components of the liver's broad, detailed and integrated response to inflammatory signals as a component of the negative acute phase response [19–21].

Inflammation-induced cholestasis is commonly caused by Lipopolysaccharide (LPS) or endotoxin released by Gram-negative bacteria, although Gram-positive and other microbial infections can also lead to cholestasis. Circulating LPS is mainly cleared by the liver, whose resident mononuclear cells (primarily Kupffer cells) produce high levels of pro-inflammatory secreted substances (cytokines). These locally-produced cytokines, in turn, activate membrane receptors of hepatocytes & cholangiocytes that transduce intracellular signals leading to altered transporter expression and function [12,15,22]. In hepatocytes, downregulation of hepatic transport systems involved in bile acid uptake and excretion, as well as downregulation of phase I and phase II detoxification systems, result in impairment in bile formation, and accumulation of bile acids and toxins in liver and serum [8,23].

The pro-inflammatory LPS-induced cytokines of most interest in these pathways are those involved in the hepatic acute phase response—Tumor Necrosis Factor alpha (TNFα), Interleukin-1 beta (IL-1β) and Interleukin-6 (IL-6) [20,21]. These and other secreted products are released by LPS-activated Kupffer cells, sinusoidal endothelial cells as wells as hepatocytes and cholangiocytes. Sepsis also induces the release of other small molecules such as nitric oxide (NO), whose production is caused by increased activity of nitric oxide synthases eNOS and iNOS in Kupffer cells and endothelial cells. NO has dual effects on the liver: low levels are hepatoprotective (they vasodilate, maintain cardiac output, prevent apoptosis, and stimulate bile flow) whereas high levels are damaging (they react with superoxide to produce radicals and promote injury, severe hypotension, vascular collapse and cholestasis). Prostaglandins are also induced by LPS in the Kupffer cells, but, ProstaglandinEs particularly have a protective role by downregulating pro-inflammatory cytokines.

Although Kupffer cells play a major role in the hepatic inflammatory reaction to LPS [24–26], other cell types contribute as well. Hepatocytes can produce cytokines [27,28] and respond with the production of acute phase proteins. Cholangiocytes produce the cytokine IL-8 and chemokine MCP1[29,30] and LPS induces IL-12 and TNFα secretion [30–32]. Altogether, the responses of the resident mononuclear cells to LPS and other microbial products, as well as the target cell's capability to recognize these products and secreted proteins, determine the degree of changes in transporter function and ultimately the degree and duration of cholestasis.

Intracellular signaling

The effects of LPS on hepatic gene expression are mediated by several parallel and intersecting intracellular signaling pathways. LPS in blood is bound to LPS Binding Protein,

which forms a complex with CD14 and MD2 to bind to the Toll-Like Receptor 4 (TLR4), expressed on multiple cell types in the liver [33]. Many downstream intracellular pathways are activated, including MAPK kinase and NFκB pathways, to regulate transporter gene expression, activity and localization.

The main effect of LPS on Kupffer cells is to activate cytokine production, via activation of NFκB and AP-1 in the nucleus of Kupffer cells. After the release of these cytokines, TNFα, IL-1β, IL-6 bind to their respective receptors on hepatocytes. This general paradigm (LPS→cytokines→activation of hepatocytic membrane cytokine receptors→ intracellular signaling cascades→ altered nuclear transcription factors→reduced transporter gene RNA expression) has been found in nearly every animal system studied, suggesting its overall applicability as a stereotyped essential biological response to inflammation.

In hepatocytes, inflammatory signals (LPS directly or indirectly through effector cytokines) reduce the expression levels of hepatocellular transporters at gene and protein levels. Studies in rodents have shown that LPS and several cytokines reduced the expression of the principal bile acid transporters Ntcp (Slc10a1) and Bsep (Abcb11), located at the basolateral and canalicular membrane respectively [34–36]. Reduced function and binding of nuclear receptors that regulate these genes appear to play major roles in this reduction of gene expression [12,18]. This is especially so for class II nuclear receptors, (which heterodimerize with RXRα) as well as for HNF1 and HNF4α. Most other transporters involved in bile formation as mentioned above are reduced under inflammatory conditions, and are regulated by these transcription factors as well. Species differences in regulation of these transporters exist, although most data is derived from studies on Ntcp, Bsep and Mrp2 (Abcc2) in rodents.

In rodents LPS treatment leads to a major reduction of both Ntcp mRNA and protein expression [35–40], which is caused by decreased binding of the nuclear transcription factors HNF1 and RXR:RAR to the rat Ntcp gene promoter [37,41,42] and of HNF1, but not RXR:RAR (so far) to the mouse Ntcp promoter [34]. Genome-wide screening for FXR binding sites discovered a potential FXR/RXR site in the mouse Ntcp promoter [43]. The regulation of Ntcp by HNF1 is influenced by HNF4α, which is upstream of HNF1 [44] and inflammatory signals have been shown to reduce HNF4α protein levels in rat liver [45] and in HepG2 cells[46], though not in mouse liver [38], via a JNK-dependent mechanism [46].

Studies with intraperitoneal injections of the cytokines TNFα, IL-1β or Il-6 have shown similar effects on Ntcp mRNA expression [34,36,38,47], whereas studies with anti-bodies against IL-1β have suggested that IL-1B may be a major regulator of Ntcp expression in vivo during inflammation [39]. Similarly, in vitro treatment with TNFα and IL-1β downregulated Ntcp promoter activity in the human cell line HepG2 [41]. In addition to Ntcp, reduced expression of HNF1 and PXR and CAR during inflammation [45,48] result in down regulation of a second set of basolateral transporters involved in bile acid uptake, the organic anion transporters Oatp1, 2, and 4 (Oatp1a1, 1a4, 1b2),. [39,48–50]. Reduced expression of human NTCP and OATP2 (OATP1B1) was also observed in liver biopsies from patients with inflammation-induced cholestasis [51] however the exact mechanism for transcriptional regulation of human NTCP has not been resolved yet.

In addition to sinusoidal effects of inflammation (lower expression and function of Ntcp and Oatp genes), reductions are also observed in the expression of Bsep and Mrp2, two major canalicular transporters responsible for bile-acid dependent and independent bile flow [37,52–54]. The rapid and profound reductions in the expression of these membrane transporter genes results in cholestasis. There is also regulation at the post-translational level[55], but the major durable effect appears to be reduced RNA transcription of these

critical determinants of bile secretion. The coordinated reduction of expression of these transporters appears to be linked to smaller nuclear quantities and altered functioning of key regulatory transcription factors, most of which are members of the nuclear receptor superfamily: HNF4α, FXR, RAR, PXR, CAR, and RXRα [18,41,56–60]. Inflammatory signaling cascades target these transcription factors, either with covalent modifications (e.g. phosphorylation), or additions of new factors in the transcription complex (e.g., phospho-c-jun, IRF3) [35,38,61–63].

Of the multiple intracellular signaling pathways activated by LPS and IL-1β, in hepatocytes JNK-mediated phosphorylation (either JNK1 or JNK2) is responsible for mediating post-translational modifications of RXRα that leads to reduction of nuclear RXRα. Since RXRα is a necessary heterodimerization partner for FXR, RAR, PXR, CAR and other nuclear receptors, its reduced function explains the rapid and coordinated suppression of hepatic transporter gene expression during LPS-induced cholestasis [35,38,62,64].

In addition to reducing RXRα protein levels and binding, LPS, TNFα or IL-1β signaling significantly decreases RNA levels of RXRα partners (FXR, CAR, PXR) and may also lead to their post-translational modification [65–67,68,69]. Similar to Ntcp, IL-1β appears to be the major regulator of Mrp2 expression during LPS-mediated inflammation since anti-IL-1β antibody pretreatment leads to preservation of Mrp2 RNA expression [39]. Thus, multiple nuclear regulators are targets for inflammation-initiated signaling all leading to coordinated changes in key transporter gene expression.

During bile acid retention from obstruction or bile acid feeding, additional sinusoidal basolateral transporters, such as Mrp3, Mrp4 and Ostα/β are expressed in order to export the accumulated excess of bile acids [7,18] Interestingly, inflammation-induced changes may dampen this increase, potentially attenuating the adaptive response and worsening bile acid retention. These effects may be species-specific since Mrp3 mRNA was induced in LPS-treated rats [70] and in HepG2 and Huh7 cells after cytokine treatment [71]. A recent study in rats suggests that Mrp4 expression is not changed by LPS treatment [72], while limited data are available for Ostα/β in inflammation. All these transporters participate in bile acid induced sinusoidal export, and if their expression is impaired by inflammation, they might not be able to adequately respond to the retained bile acid load, and thus may worsen bile acid-related hepatic injury.

New mechanisms for crosstalk between inflammation and nuclear regulators

Recent findings that NFκB interacts with nuclear receptors, specifically FXR and PXR, has expanded our knowledge but also added complexity to the regulation of transporters during inflammatory conditions [73,74]. The results of these studies suggest a reciprocal interaction between NFκB and FXR when activated by inflammation or ligand, respectively: NFκB activation by LPS antagonizes FXR activity and suggests an anti-inflammatory role for FXR, where FXR activation inhibits NFκB. Indeed, LPS-induced cytokine expression was markedly enhanced in FXR knockout mice.

Cholestatic inflammatory responses of the liver are not restricted to hepatocytes, as bile duct inflammatory responses also occur. Il-1β induces proteasomal degradation of Asbt in cholangiocytes [75] via JNK-dependent phosphorylation of Asbt. No data is available on regulatory mechanisms, nor what happens to the transporters Ae2 and Cftr.

Clinical manifestations and inter-relations between inflammation and cholestasis

There are many, clinically relevant situations where inflammation either causes, or contributes, to cholestatic liver diseases. Some of these are clearly linked (e.g. PSC, AIH or sepsis) while others are most likely indirect effects (e.g., drugs, post-transplant rejection, total parental nutrition (TPN), or systemic conditions such as rheumatoid arthritis). In addition, recent studies have suggested that bile acids themselves may act as anti-inflammatory agents via bile acid bound nuclear receptors, akin to glucocorticoids and mediated by glucocorticoid receptors [73]. Overall, given the liver's central role in innate immunity, front-line host defense against invaders and xenobiotics, it is not surprising that the liver can elaborate a complex, interrelated response to inflammation. Part of this responsiveness is the liver's role in the Acute Phase Response, which is the body's combined "early warning system" and "rapid responder" to injury and infection where a multitude of antimicrobial, anti-oxidant and restorative compounds and proteins are secreted into the systemic circulation. Thus the clinical course and outcome for patients with liver diseases may be dependent on the balance of the liver's secreted, local, and intracellular responses to inflammation and cholestasis.

Sepsis-associated cholestasis

It has been known for many years that patients with a wide variety of non-hepatic infections can develop cholestasis (see [15,76] for excellent reviews). In 1901, in his classic textbook The Principles and Practice of Medicine, Osler reports that pneumonia can lead to jaundice ("toxaemic jaundice") [77], and notes that:

> In this form there is no obstruction in the bile-passages, but the jaundice is associated with toxic states of the blood, dependent upon various poisons which either act directly on the blood itself, or in some cases on the liver-cells as well.

It is not uncommon to find elevated conjugated bilirubin levels in patients with various infections, with the common ones being gut-derived organisms (gram negative predominantly but not exclusively), but also from viral infections. In infants, especially in newborns, sepsis can present first with increasing jaundice [78,79]. Sepsis-associated jaundice is seen in adults with significant frequency. Fore example, patients presenting to an Emergency Center for jaundice in South West Wales were due to malignancy, sepsis and cirrhosis, in that order [80].

Several lines of evidence suggest that Osler's "various poisons" that link infection to cholestasis are either cytokines (mainly TNFα, IL-1β, IL-6) or microbial TLR2 or TLR4 agonists[15,81]. Liver targets primarily include hepatocytes, but also extend to cholangiocytes, endothelial cells and stellate cells. There are no direct studies of bile flow in humans given endotoxin, but there is sufficient indirect evidence to link endotoxin and endotoxin-induced cytokines, to cholestasis [82,83]. In frank sepsis, including septic shock, hyperbilirubinemia is usually a central clinical finding, often out of proportion to typically mild elevations in serum transaminase [84]. Some humans who have been given long-term infusions of TNFα, reportedly have experienced significant hyperbilirubinemia [85]. In addition, single infusions of recombinant human TNFα can lead to conjugated hyperbilirubinemia—further supporting a link between cytokines and cholestasis [86].

Conjugated hyperbilirubinemia is the most typical clinical finding in sepsis because it is always included in standard laboratory analyses. However serum bile acids are also elevated in sepsis and perhaps and are most likely related to altered expression of bile acid

transporters seen in animal models. A systematic exploration of bile acid flux in septic humans has not been reported.

TPN associated cholestasis (TPNAC)

TPNAC is one of the most serious clinical scenarios where cholestasis occurs rapidly and is highly linked with early death [87,88]. Infants, who are usually premature and who have had gut resections are dependent upon TPN for growth and frequently develop cholestasis that rapidly progresses to fibrosis, cirrhosis and portal hypertension, usually before 6 months of life. The degree of cholestasis and chance of survival in these infants have been linked to the number of septic episodes, likely initiated by recurrent bacterial translocation across their gut mucosa. Although there are also cholestatic effects from the intravenous formulation in these infants, [89,90] septic mediators likely contribute the most to altered hepatic function [91]. Interestingly, a case report of a patient with Crohn Disease who developed cholestasis on TPN, resolved after treatment with infliximab (anti-TNFα antibody) infusions. [92].

Infants

Upwards of 25–30% of septic newborn infants present with jaundice for reasons likely related to immaturity of the immune system and liver function [78,79]. In some instances, an abrupt increase in visible jaundice develops when sepsis-associated conjugated hyperbilirubinemia occurs on top of a pre-existing physiological unconjugated hyperbilirubinemia of infancy, or breast milk-associated jaundice [93]. Regardless of the underlying precipitant, cholestasis is more likely to occur in this patient population in response to sepsis. Few investigative studies have been directly performed in infants that quantify the degree, and duration of the immaturity of their hepatobiliary excretory function. Such “physiologic cholestasis” is mostly evident during the first few months of life and is associated with elevated serum bile acid levels and lower bile acid pool sizes [94]. Thus at this age, infections are most likely to suppress bile flow further, thereby leading to a greater incidence of sepsis-associated cholestasis.

Adult hepatic inflammatory diseases

A few studies have explored the regulation of transporter genes in inflammation-based human cholestatic diseases, namely primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) [23]. In inflammation induced cholestasis (mainly due to alcohol) Bsep, Ntcp and Oatp2 gene expression were suppressed, while Mrp2 protein, but not Mrp2 RNA levels, were reduced [51]. Interestingly, as PBC progresses, several changes occur that appear to help unload the liver of retained bile acids [95]. Ntcp and Oatp2 RNA levels are reduced, while the exporter, Mrp3, is increased. possibly influenced by ursodeoxycholic acid therapy in these samples, an effect which could not be determined. Ostα and Ostβ RNA levels are upregulated in later stage PBC, likely a result of retained bile acids and FXR-mediated induction of transcription [96]. Thus, ability of retained bile acids to drive Bsep expression still seems to be preserved in later stage PBC. One study has been published reporting transporter RNA levels in PSC, where reduced levels of Oatp2 and Mrp2 were noted in liver samples[97]. Similar studies will need to be performed in the future to better define the pattern of transporter responses to cholestasis in these inflammatory cholangiopathies.

Cholestasis altering the systemic inflammatory conditions

In addition to the role of sepsis in the pathogenesis of cholestasis, there are also intriguing, and recently evolving, mechanistic linkages suggesting that cholestasis reduces inflammation [73,98]. Clinicians have noted for > 100 years that certain systemic inflammatory conditions may temporarily subside during episodes of hepatitis [99]. In 1897, Still noted that

joint symptoms subsided during a bout of hepatitis in a patient with rheumatoid arthritis, while Hench at the Mayo Clinic compiled a series of 19 cases, noting that the joint improvement correlated most with increasing jaundice[100,101]. He and others considered that there was an anti-inflammatory component of bile, perhaps bile acids, and tried to replicate the phenomenon with infusions of bile acids or infected sera. None of these limited studies were convincing although there were a few patients whose joint symptoms transiently improved. Recent laboratory studies with human monocytes in culture demonstrated that incubations with bile acids reduced cytokine expression [102]. The degree to which bile acids suppress inflammation in human liver diseases remains to be determined, but uncovering these pathways in animal models and human cells, may at least lead to ways to modify the effects of inflammation on the liver.

Therapeutic interventions and rational targets

Successful interventions with appropriate antimicrobials that counteract the cause of liver injury in sepsis usually lead to resolution of the hepatobiliary impairments including cholestasis. Resumption of full enteral feeding to infants with TPNAC typically leads to normalization of serum conjugated bilirubin and bile acid levels within weeks. In subjects whose cholestasis was the direct consequence of pro-inflammatory cytokine infusions, their cholestasis subsided soon after the infusions ended. However, the problems associated with chronic inflammatory conditions (e.g. PBC and PSC) continue, typically because of a lack of effective medical therapy. It is in these conditions that new therapeutics, perhaps involving nuclear receptors [17] may hold promise. For these two diseases, as well as biliary atresia, standard anti-inflammatory agents (glucocorticoids) have been proven to be ineffective. Thus, other targets and agents need to be explored in order to find effective means to rationally intervene.

Abbreviations

LPS	Lipopolysaccharide
TNFα	Tumor Necrosis Factor alpha
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
NO	Nitric Oxide
NOS	nitric oxide synthase
NFκB	nuclear factor kappa B
Bsep/Abcb11	Bile salt export pump
Ntcp/Slc10a1	Sodium taurocholate co-transporting polypeptide
HNF	Hepatocyte nuclear factor
RXR	Retinoid X receptor
Mrp2-4/Abcc2-4	multidrug resistance-associated protein 2-4
RAR	Retinoic acid receptor
JNK	cJun N-terminal kinase
PXR	Pregnane X receptor
CAR	Constitutive androstane receptor

FXR	Farnesoid X receptor
OATP/SLCO	Organic anion transport polypeptide
PBC	Primary Biliary Cirrhosis
PSC	Primary Sclerosing Cholangitis
TPN	total parental nutrition
TLR	Toll-like receptor
TPNAC	TPN associated cholestasis

References

1. Copple BLJH, Klaassen CD. Oxidative stress and the pathogenesis of cholestasis. Seminars in Liver Disease 2010. 2010; 30(2) In press.
2. Davit-Spraul AGE, Baussan C, Jacquemin E. The spectrum of liver diseases related to ABCB4 gene mutations: Pathophysiology and clinical aspects. Seminars in Liver Disease. 2010; 30(2) In press.
3. Pauli-Magnus CMP, Stieger B. Genetic determinants of drug induced cholestasis and Intrahepatic Cholestasis of Pregnancy. Seminars in Liver Disease. 2010; 30(2) In press.
4. Paulusma CCOER, Jansen PLM. Progressive familial intrahepatic cholestasis type 1. Seminars in Liver Disease. 2010; 30(2) In press.
5. Ping Lam PCJSC, Boyer JL. The bile salt export pump: Clinical and experimental aspects of genetic and acquired cholestatic liver disease. Seminars in Liver Disease. 2010; 30(2) In press.
6. Soroka CJBN, Boyer JL. Organic solute transporter, OSTalpha-OSTbeta: Its role in bile acid transport and cholestasis. Seminars in Liver Disease. 2010; 30(2) In press.
7. Wagner MZG, Trauner M. Nuclear receptor regulation of the adaptive response of bile acid transporters in cholestasis. Seminars in Liver Disease. 2010; 30(2) In press.
8. Wagner M, Zollner G, Trauner M. New molecular insights into the mechanisms of cholestasis. J Hepatol. 2009; 51(3):565–580. [PubMed: 19595470]
9. Zollner G, Trauner M. Nuclear receptors as therapeutic targets in cholestatic liver diseases. Br J Pharmacol. 2009; 156(1):7–27. [PubMed: 19133988]
10. Stahl S, Davies MR, Cook DI, Graham MJ. Nuclear hormone receptor-dependent regulation of hepatic transporters and their role in the adaptive response in cholestasis. Xenobiotica. 2008; 38(7–8):725–777. [PubMed: 18668429]
11. Kosters A, Karpen SJ. Bile acid transporters in health and disease. Xenobiotica. 2008; 38(7–8): 1043–1071. [PubMed: 18668439]
12. Mulder J, Karpen SJ, Tietge UJ, Kuipers F. Nuclear receptors: mediators and modifiers of inflammation-induced cholestasis. Front Biosci. 2009; 14:2599–2630.
13. Dawson PA, Lan T, Rao A. Bile acid transporters. J Lipid Res. 2009; 50(12):2340–2357. [PubMed: 19498215]
14. Teng S, Piquette-Miller M. Regulation of transporters by nuclear hormone receptors: implications during inflammation. Mol Pharm. 2008; 5(1):67–76. [PubMed: 18072749]
15. Geier A, Fickert P, Trauner M. Mechanisms of disease: mechanisms and clinical implications of cholestasis in sepsis. Nat Clin Pract Gastroenterol Hepatol. 2006; 3(10):574–585. [PubMed: 17008927]
16. Geier A, Wagner M, Dietrich CG, Trauner M. Principles of hepatic organic anion transporter regulation during cholestasis, inflammation and liver regeneration. Biochim Biophys Acta. 2007; 1773(3):283–308. [PubMed: 17291602]
17. Karpen SJ, Trauner M. The new therapeutic frontier - Nuclear receptors and the liver. Journal of hepatology. 2009

18. Zollner G, Marschall HU, Wagner M, Trauner M. Role of nuclear receptors in the adaptive response to bile acids and cholestasis: pathogenetic and therapeutic considerations. Mol Pharm. 2006; 3(3):231–251. [PubMed: 16749856]
19. Moshage H. Cytokines and the hepatic acute phase response. Journal of Pathology. 1997; 181(3): 257–266. [PubMed: 9155709]
20. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999; 340(6):448–454. [PubMed: 9971870]
21. Baumann H, Gauldie J. The acute phase response. Immunol Today. 1994; 15(2):74–80. [PubMed: 7512342]
22. Trauner M, Fickert P, Stauber R. Inflammation-induced cholestasis. J Gastroenterol Hepatol. 1999; 14(10):946–959. [PubMed: 10530489]
23. Trauner M, Wagner M, Fickert P, Zollner G. Molecular regulation of hepatobiliary transport systems: clinical implications for understanding and treating cholestasis. J Clin Gastroenterol. 2005; 39(4 Suppl 2):S111–124. [PubMed: 15758646]
24. Nakamura J, Nishida T, Hayashi K, et al. Kupffer cell-mediated down regulation of rat hepatic CMOAT/MRP2 gene expression. Biochem Biophys Res Commun. 1999; 255(1):143–149. [PubMed: 10082670]
25. Xu DX, Wei W, Sun MF, et al. Kupffer cells and reactive oxygen species partially mediate lipopolysaccharide-induced downregulation of nuclear receptor pregnane x receptor and its target gene CYP3a in mouse liver. Free Radic Biol Med. 2004; 37(1):10–22. [PubMed: 15183191]
26. Sturm E, Havinga R, Baller JF, et al. Kupffer cell depletion with liposomal clodronate prevents suppression of Ntcp expression in endotoxin-treated rats. J Hepatol. 2005; 42(1):102–109. [PubMed: 15629514]
27. Ohlinger W, Dinges HP, Zatloukal K, et al. Immunohistochemical detection of tumor necrosis factor-alpha, other cytokines and adhesion molecules in human livers with alcoholic hepatitis. Virchows Arch A Pathol Anat Histopathol. 1993; 423(3):169–176. [PubMed: 7694422]
28. Luster MI, Germolec DR, Yoshida T, Kayama F, Thompson M. Endotoxin-induced cytokine gene expression and excretion in the liver. Hepatology. 1994; 19(2):480–488. [PubMed: 8294104]
29. Morland CM, Fear J, McNab G, Joplin R, Adams DH. Promotion of leukocyte transendothelial cell migration by chemokines derived from human biliary epithelial cells in vitro. Proc Assoc Am Physicians. 1997; 109(4):372–382. [PubMed: 9220535]
30. Fava G, Glaser S, Francis H, Alpini G. The immunophysiology of biliary epithelium. Semin Liver Dis. 2005; 25(3):251–264. [PubMed: 16143942]
31. Harada K, Ohira S, Isse K, et al. Lipopolysaccharide activates nuclear factor-kappaB through toll-like receptors and related molecules in cultured biliary epithelial cells. Lab Invest. 2003; 83(11): 1657–1667. [PubMed: 14615419]
32. Chen XM, O'Hara SP, LaRusso NF. The immunobiology of cholangiocytes. Immunol Cell Biol. 2008; 86(6):497–505. [PubMed: 18504452]
33. Seki E, Brenner D. Toll-like receptors and adaptor molecules in liver disease: update. Hepatology. 2008; 48(1):322–335. [PubMed: 18506843]
34. Geier A, Dietrich CG, Voigt S, et al. Cytokine-dependent regulation of hepatic organic anion transporter gene transactivators in mouse liver. Am J Physiol Gastrointest Liver Physiol. 2005; 289(5):G831–841. [PubMed: 15860642]
35. Ghose R, Zimmerman TL, Thevananther S, Karpen SJ. Endotoxin leads to rapid subcellular re-localization of hepatic RXRalpha: A novel mechanism for reduced hepatic gene expression in inflammation. Nucl Recept. 2004; 2(1):4. [PubMed: 15312234]
36. Green RM, Beier D, Gollan JL. Regulation of hepatocyte bile salt transporters by endotoxin and inflammatory cytokines in rodents. Gastroenterology. 1996; 111(1):193–198. [PubMed: 8698199]
37. Trauner M, Arrese M, Lee H, Boyer JL, Karpen SJ. Endotoxin downregulates rat hepatic ntcp gene expression via decreased activity of critical transcription factors. J Clin Invest. 1998; 101(10): 2092–2100. [PubMed: 9593765]
38. Kosters A, White DD, Sun H, Thevananther S, Karpen SJ. Redundant roles for cJun-N-terminal kinase 1 and 2 in interleukin-1beta-mediated reduction and modification of murine hepatic nuclear retinoid X receptor alpha. J Hepatol. 2009; 51(5):898–908. [PubMed: 19767119]

39. Geier A, Dietrich CG, Voigt S, et al. Effects of proinflammatory cytokines on rat organic anion transporters during toxic liver injury and cholestasis. Hepatology. 2003; 38(2):345–354. [PubMed: 12883478]
40. Kim PK, Chen J, Andrejko KM, Deutschman CS. Intraabdominal sepsis down-regulates transcription of sodium taurocholate cotransporter and multidrug resistance-associated protein in rats. Shock. 2000; 14(2):176–181. [PubMed: 10947163]
41. Denson LA, Auld KL, Schiek DS, et al. Interleukin-1beta suppresses retinoid transactivation of two hepatic transporter genes involved in bile formation. J Biol Chem. 2000; 275(12):8835–8843. [PubMed: 10722729]
42. Karpen SJ, Sun AQ, Kudish B, et al. Multiple factors regulate the rat liver basolateral sodium-dependent bile acid cotransporter gene promoter. J Biol Chem. 1996; 271(25):15211–15221. [PubMed: 8662994]
43. Thomas AM, Hart SN, Kong B, et al. Genome-wide tissue-specific farnesoid X receptor binding in mouse liver and intestine. Hepatology (Baltimore, Md). 2009
44. Miura N, Tanaka K. Analysis of the rat hepatocyte nuclear factor (HNF) 1 gene promoter: synergistic activation by HNF4 and HNF1 proteins. Nucleic Acids Res. 1993; 21(16):3731–3736. [PubMed: 8367288]
45. Wang B, Cai SR, Gao C, Sladek FM, Ponder KP. Lipopolysaccharide results in a marked decrease in hepatocyte nuclear factor 4 alpha in rat liver. Hepatology. 2001; 34(5):979–989. [PubMed: 11679969]
46. Li T, Jahan A, Chiang JY. Bile acids and cytokines inhibit the human cholesterol 7 alpha-hydroxylase gene via the JNK/c-jun pathway in human liver cells. Hepatology. 2006; 43(6):1202–1210. [PubMed: 16729332]
47. Siewert E, Dietrich CG, Lammert F, et al. Interleukin-6 regulates hepatic transporters during acute-phase response. Biochem Biophys Res Commun. 2004; 322(1):232–238. [PubMed: 15313196]
48. Li N, Klaassen CD. Role of liver-enriched transcription factors in the down-regulation of organic anion transporting polypeptide 4 (oatp4; oatplb2; slc21a10) by lipopolysaccharide. Mol Pharmacol. 2004; 66(3):694–701. [PubMed: 15322262]
49. Hartmann G, Cheung AK, Piquette-Miller M. Inflammatory cytokines, but not bile acids, regulate expression of murine hepatic anion transporters in endotoxemia. J Pharmacol Exp Ther. 2002; 303(1):273–281. [PubMed: 12235261]
50. Cherrington NJ, Slitt AL, Li N, Klaassen CD. Lipopolysaccharide-mediated regulation of hepatic transporter mRNA levels in rats. Drug Metab Dispos. 2004; 32(7):734–741. [PubMed: 15205389]
51. Zollner G, Fickert P, Zenz R, et al. Hepatobiliary transporter expression in percutaneous liver biopsies of patients with cholestatic liver diseases. Hepatology. 2001; 33(3):633–646. [PubMed: 11230744]
52. Trauner M. Molecular alterations of canalicular transport systems in experimental models of cholestasis: possible functional correlations. Yale J Biol Med. 1997; 70(4):365–378. [PubMed: 9626757]
53. Trauner M, Nathanson MH, Rydberg SA, et al. Endotoxin impairs biliary glutathione and HCO3- excretion and blocks the choleretic effect of nitric oxide in rat liver. Hepatology. 1997; 25(5): 1184–1191. [PubMed: 9141437]
54. Geier A, Zollner G, Dietrich CG, et al. Cytokine-independent repression of rodent Ntcp in obstructive cholestasis. Hepatology. 2005; 41(3):470–477. [PubMed: 15723437]
55. Kubitz R, Wettstein M, Warskulat U, Haussinger D. Regulation of the multidrug resistance protein 2 in the rat liver by lipopolysaccharide and dexamethasone. Gastroenterology. 1999; 116(2):401–410. [PubMed: 9922322]
56. Ananthanarayanan M, Balasubramanian N, Makishima M, Mangelsdorf DJ, Suchy FJ. Human bile salt export pump promoter is transactivated by the farnesoid X receptor/bile acid receptor. J Biol Chem. 2001; 276(31):28857–28865. [PubMed: 11387316]
57. Gerloff T, Geier A, Roots I, Meier PJ, Gartung C. Functional analysis of the rat bile salt export pump gene promoter. Eur J Biochem. 2002; 269(14):3495–3503. [PubMed: 12135489]

58. Kast HR, Goodwin B, Tarr PT, et al. Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. J Biol Chem. 2002; 277(4):2908–2915. [PubMed: 11706036]
59. Plass JR, Mol O, Heegsma J, et al. Farnesoid X receptor and bile salts are involved in transcriptional regulation of the gene encoding the human bile salt export pump. Hepatology. 2002; 35(3):589–596. [PubMed: 11870371]
60. Karpen SJ. Nuclear receptor regulation of hepatic function. J Hepatol. 2002; 36(6):832–850. [PubMed: 12044537]
61. Beigneux AP, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. The acute phase response is associated with retinoid X receptor repression in rodent liver. J Biol Chem. 2000; 275(21):16390–16399. [PubMed: 10747970]
62. Zimmerman TL, Thevananther S, Ghose R, Burns AR, Karpen SJ. Nuclear export of retinoid X receptor alpha in response to interleukin-1beta-mediated cell signaling: roles for JNK and SER260. J Biol Chem. 2006; 281(22):15434–15440. [PubMed: 16551633]
63. Hisaeda K, Inokuchi A, Nakamura T, et al. Interleukin-1beta represses MRP2 gene expression through inactivation of interferon regulatory factor 3 in HepG2 cells. Hepatology. 2004; 39(6): 1574–1582. [PubMed: 15185298]
64. Li D, Zimmerman TL, Thevananther S, et al. Interleukin-1 beta-mediated suppression of RXR:RAR transactivation of the Ntcp promoter is JNK-dependent. J Biol Chem. 2002; 277(35): 31416–31422. [PubMed: 12105223]
65. Kim MS, Shigenaga J, Moser A, Feingold K, Grunfeld C. Repression of farnesoid X receptor during the acute phase response. J Biol Chem. 2003; 278(11):8988–8995. [PubMed: 12519762]
66. Fang C, Yoon S, Tindberg N, et al. Hepatic expression of multiple acute phase proteins and down-regulation of nuclear receptors after acute endotoxin exposure. Biochem Pharmacol. 2004; 67(7): 1389–1397. [PubMed: 15013855]
67. Beigneux AP, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. Reduction in cytochrome P-450 enzyme expression is associated with repression of CAR (constitutive androstane receptor) and PXR (pregnane X receptor) in mouse liver during the acute phase response. Biochem Biophys Res Commun. 2002; 293(1):145–149. [PubMed: 12054576]
68. Teng S, Piquette-Miller M. The involvement of the pregnane X receptor in hepatic gene regulation during inflammation in mice. J Pharmacol Exp Ther. 2005; 312(2):841–848. [PubMed: 15456840]
69. Frankenberg T, Miloh T, Chen F, et al. The membrane protein ATPase class I type 8B member 1 signals through protein kinase C zeta to activate the farnesoid X receptor. Hepatology. 2008
70. Donner MG, Warskulat U, Saha N, Haussinger D. Enhanced expression of basolateral multidrug resistance protein isoforms Mrp3 and Mrp5 in rat liver by LPS. Biol Chem. 2004; 385(3–4):331–339. [PubMed: 15134348]
71. Lee G, Piquette-Miller M. Cytokines alter the expression and activity of the multidrug resistance transporters in human hepatoma cell lines; analysis using RT-PCR and cDNA microarrays. J Pharm Sci. 2003; 92(11):2152–2163. [PubMed: 14603501]
72. Brcakova E, Fuksa L, Cermanova J, et al. Alteration of methotrexate biliary and renal elimination during extrahepatic and intrahepatic cholestasis in rats. Biol Pharm Bull. 2009; 32(12):1978–1985. [PubMed: 19952415]
73. Wang YD, Chen WD, Wang M, et al. Farnesoid X receptor antagonizes nuclear factor kappaB in hepatic inflammatory response. Hepatology. 2008; 48(5):1632–1643. [PubMed: 18972444]
74. Zhou C, Tabb MM, Nelson EL, et al. Mutual repression between steroid and xenobiotic receptor and NF-kappaB signaling pathways links xenobiotic metabolism and inflammation. J Clin Invest. 2006; 116(8):2280–2289. [PubMed: 16841097]
75. Xia X, Roundtree M, Merikhi A, et al. Degradation of the apical sodium-dependent bile acid transporter by the ubiquitin-proteasome pathway in cholangiocytes. J Biol Chem. 2004; 279(43): 44931–44937. [PubMed: 15304498]
76. Chand N, Sanyal A. Sepsis-induced cholestasis. Hepatology. 2007; 45(1):230–241. [PubMed: 17187426]
77. Osler, W. Principles and Practice of Medicine. 1901. p. 550

78. Dunham EC. Septicemia in the newborn. American Journal of the Diseases of Children. 1933; 45(2):229–253.
79. BERNSTEIN J, BROWN AK. Sepsis and jaundice in early infancy. Pediatrics. 1962; 29:873–882. [PubMed: 13868269]
80. Whitehead M, Hainsworth I, Kingham J. The causes of obvious jaundice in South West Wales: perceptions versus reality. Gut. 2001; 48(3):409–413. [PubMed: 11171834]
81. Moseley R. Sepsis and cholestasis. Clin Liver Dis. 2004; 8(1):83–94. [PubMed: 15062195]
82. Bahador M, Cross AS. From therapy to experimental model: a hundred years of endotoxin administration to human subjects. J Endotoxin Res. 2007; 13(5):251–279. [PubMed: 17986486]
83. Santos A, Wilmore D. The systemic inflammatory response: perspective of human endotoxemia. Shock. 1996; 6(Suppl 1):S50–56. [PubMed: 8828098]
84. Pastor CM, Suter PM. Hepatic hemodynamics and cell functions in human and experimental sepsis. Anesth Analg. 1999; 89(2):344–352. [PubMed: 10439746]
85. Sherman M, Spriggs D, Arthur K, et al. Recombinant human tumor necrosis factor administered as a five-day continuous infusion in cancer patients: phase I toxicity and effects on lipid metabolism. Journal of Clinical Oncology. 1988; 6(2):344–350. [PubMed: 3339398]
86. Jones A, Selby PJ, Viner C, et al. Tumour necrosis factor, cholestatic jaundice, and chronic liver disease. Gut. 1990; 31(8):938–939. [PubMed: 2387521]
87. Carter B, Karpen S. Intestinal failure-associated liver disease: management and treatment strategies past, present, and future. Semin Liver Dis. 2007; 27(3):251–258. [PubMed: 17682972]
88. Spencer A, Neaga A, West B, et al. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg. 2005; 242(3):403–409. discussion 409–412. [PubMed: 16135926]
89. Gura K, Duggan C, Collier S, et al. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics. 2006; 118(1):e197–201. [PubMed: 16818533]
90. Soden JS, Lovell MA, Brown K, Partrick DA, Sokol RJ. Failure of Resolution of Portal Fibrosis during Omega-3 Fatty Acid Lipid Emulsion Therapy in Two Patients with Irreversible Intestinal Failure. J Pediatr. 2010; 156(2):327–331. [PubMed: 20105644]
91. Beath S, Davies P, Papadopoulou A, et al. Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. J Pediatr Surg. 1996; 31(4):604–606. [PubMed: 8801324]
92. Forrest EH, Oien KA, Dickson S, Galloway D, Mills PR. Improvement in cholestasis associated with total parenteral nutrition after treatment with an antibody against tumour necrosis factor alpha. Liver. 2002; 22(4):317–320. [PubMed: 12296965]
93. ARIAS IM, GARTNER LM, SEIFTER S, FURMAN M. PROLONGED NEONATAL UNCONJUGATED HYPERBILIRUBINEMIA ASSOCIATED WITH BREAST FEEDING AND A STEROID, PREGNANE-3(ALPHA), 20(BETA)-DIOL, IN MATERNAL MILK THAT INHIBITS GLUCURONIDE FORMATION IN VITRO. J Clin Invest. 1964; 43:2037–2047. [PubMed: 14228539]
94. Heubi J, Balistreri W, Suchy F. Bile salt metabolism in the first year of life. Journal of Laboratory & Clinical Medicine. 1982; 100(1):127–136. [PubMed: 7201000]
95. Zollner G, Fickert P, Silbert D, et al. Adaptive changes in hepatobiliary transporter expression in primary biliary cirrhosis. J Hepatol. 2003; 38(6):717–727. [PubMed: 12763363]
96. Boyer J, Trauner M, Mennone A, et al. Upregulation of a basolateral FXR-dependent bile acid efflux transporter OST{alpha}-OSTbeta in cholestasis in humans and rodents. Am J Physiol Gastrointest Liver Physiol. 2006; 290(6):G1124–1130. [PubMed: 16423920]
97. Oswald M, Kullak-Ublick G, Paumgartner G, Beuers U. Expression of hepatic transporters OATP-C and MRP2 in primary sclerosing cholangitis. Liver. 2001; 21(4):247–253. [PubMed: 11454187]
98. Wagner M, Zollner G, Trauner M. Nuclear bile acid receptor farnesoid X receptor meets nuclear factor-kappaB: new insights into hepatic inflammation. Hepatology. 2008; 48(5):1383–1386. [PubMed: 18972560]
99. Wishart J. A link between rheumatoid arthritis and jaundice. British Medical Journal. 1903; 1:252.

100. HENCH P. EFFECT OF JAUNDICE ON CHRONIC INFECTIOUS (ATROPHIC) ARTHRITIS AND ON PRIMARY FIBROSITIS: FURTHER OBSERVATIONS; ATTEMPTS TO REPRODUCE THE PHENOMENON. Arch Intern Med. 1938; 61(3):451–480.

101. Hench P. Recent Investigations on Rheumatism and Arthritis in the United States. Ann Rheum Dis. 1940; 2(1):19–40. [PubMed: 18623657]

102. Calmus Y, Guechot J, Podevin P, et al. Differential effects of chenodeoxycholic and ursodeoxycholic acids on interleukin 1, interleukin 6 and tumor necrosis factor-alpha production by monocytes. Hepatology. 1992; 16(3):719–723. [PubMed: 1505915]