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REGULATION OF DRUG-METABOLIZING ENZYMES AND TRANSPORTERS IN INFLAMMATION

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■ **Abstract** Inflammation and infection have long been known to downregulate the activity and expression of cytochrome P450 (CYP) enzymes involved in hepatic drug clearance. This can result in elevated plasma drug levels and increased adverse effects. Recent information on regulation of human CYP enzymes is presented, as are new developments in our understanding of the mechanisms of regulation. Experiments to study the effects of modulating CYP activities on the inflammatory response have yielded possible insights into the physiological consequences, if not the purpose, of the downregulation. Regulation of hepatic flavin monooxygenases, UDP-glucuronosyltransferases, sulfotransferases, glutathione S-transferases, as well as of hepatic transporters during the inflammatory response, exhibits similarities and differences with regulation of CYPs.

INTRODUCTION

The liver is the major site of drug clearance from the circulation, and it expresses numerous drug-metabolizing enzymes (DMEs), including the cytochrome P450 (CYP) (1), flavin monooxygenase (FMO) (2), UDP-glucuronosyltransferase (UGT) (3), sulfotransferase (SULT) (4), and glutathione S-transferase (GST) (5) families, as well as uptake and efflux transporters that also have important roles in drug disposition and clearance. The regulation of CYP enzymes in models of infectious and inflammatory disease has been studied for 30 years, and has been described in several recent reviews (6–10). The majority of activities and enzymes are downregulated, and this can lead to decreased drug clearance, elevations of plasma drug levels, and drug toxicity. Conversely, downregulation of CYPs can protect from toxicity of compounds that are bioactivated by these enzymes (6–10).

The reader is referred to previous reviews for more comprehensive coverage of earlier clinical studies in this area (6, 9, 10). From these, and the highlighted

recent studies below, it is apparent that infection or inflammation can decrease metabolic clearance of CYP substrates by 20%–70%. Obviously, the potential for clinically relevant consequences of these changes will be highest when large changes in clearance occur, and with drugs that have a low safety margin. However, the impact of infectious or inflammatory diseases must be considered in the context of other factors that affect an individual's CYP activity and drug clearance, such as genetic polymorphisms and concomitant drug therapy (Figure 1). Thus, the effects of an infection and, for example, daily use of a herbal product containing CYP inhibitors in a patient with a genetic polymorphism in a specific CYP enzyme, could combine geometrically to profoundly reduce drug clearance and increase plasma drug levels.

Other hepatic DMEs, as well as transporters, are regulated during inflammation and infection, with corresponding consequences for drug metabolism and transport. The same major questions arise in these fields as for the CYPs: What are the consequences for drug disposition, therapeutic effect, and toxicity in humans? Are family members regulated coordinately or differentially? Is the response important for homeostasis, or is it an epiphenomenon? What cytokines and cell types are involved, and what are the cellular and molecular mechanisms? These are the questions that we address in the ensuing discussion in which we reveal commonalities and differences that are emerging in the factors and mechanisms that regulate hepatic DMEs and transporters. We recognize that DMEs and transporters are

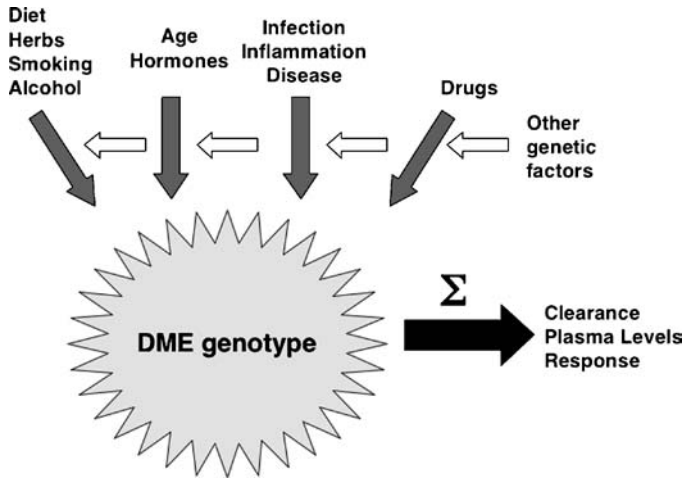

Figure 1 Integration of genetic, physiological, and environmental influences on drug metabolism and clearance. Effects of inflammation, infection, concomitant drug therapy, environmental, and lifestyle factors on DME activity are superimposed upon genetic polymorphisms affecting enzyme function, basal, and induced expression. The responses to the epigenetic factors can themselves be modified by polymorphisms in receptors and signaling pathways required for the responses.

also regulated in extrahepatic tissues, but to focus the discussion we only refer to extrahepatic regulation if a specific point is to be made.

REGULATION OF CYP ENZYMES

Experimental Animals

The phenomenon of CYP regulation by inflammation in experimental animals has been studied extensively (6–10). In the best-studied model of inflammation, that of bacterial endotoxin (lipopolysaccharide, LPS) exposure, most CYPs are downregulated, but a few are unaffected or even induced. For example, we observed the downregulation of mRNAs for CYP1A2, 2A5, 2C29, 2E1, 3A11, 4A10, and 4A14 in livers of LPS-treated mice, whereas CYP3A13 mRNA was unaffected (11). Previous studies had shown that CYP4A mRNAs are induced in rat livers (12), but they are downregulated in mice (13). Fang et al. (14) recently reported the downregulation of several CYP and other DME genes using low-density microarrays, 4 h after LPS treatment of rats. Long-term (12 h to days) changes in P450-dependent activities are accompanied by changes in microsomal concentrations of CYP enzymes, which are usually (but not always) explained by prior changes in the corresponding mRNAs (6–10). Short-term (a few hours) decreases in CYP activity can occur in the absence of detectable changes in the corresponding proteins (6–10), and possible mechanisms of these effects are discussed below.

Many of the in vivo effects of inflammation are due to circulating or Kupffer cell-derived proinflammatory cytokines because these agents can recapitulate the effects of inflammatory stimuli when injected in vivo or incubated with hepatocytes (6–10). Different cytokines regulate different CYPs, and there is generally good correlation between their in vivo and in vitro effects (6–10). This suggests that the specificity of CYP regulation may be different in different models of infection and inflammation, in which the profile, time course, and sources of cytokines are different. The ensuing discussion illustrates the need for systematic comparisons of CYP (and other DME and transporter) gene expression in different models of infection and inflammation using gene array and proteomic technology. Although much has been learned using LPS and other sterile models, more work is needed with live models of infection that are multifactorial and more accurately reflect clinical situations.

Subcutaneous injection of turpentine is another well-characterized model of aseptic inflammation, although it has not been as well studied for regulation of CYP enzymes. Siewert et al. (15) found that mouse hepatic CYP 1A2, 2A5, 2E1, and 3A11 mRNAs were each downregulated in both LPS and turpentine-treated mice, although there were significant differences in the magnitudes and time courses of the responses. This is in agreement with our studies using other sterile irritants in rats (16, 17).

Two laboratories have demonstrated that inflammation of the CNS caused by intracerebroventricular (icv) injection of LPS not only regulates CYP expression

in the CNS, but also in the liver and kidneys (10, 18). The effects on hepatic CYP expression are very similar to those caused by systemic LPS injection, and they are accompanied by elevations in serum cytokines (10). Very recently, it was found that the regulation of CYPs in peripheral tissues in this model requires the LPS receptor toll-like receptor-4, and is likely due to transfer of LPS from the brain to the serum (19).

Infection of rats with a model recombinant adenoviral vector produced a dose-dependent suppression of CYP3A mRNA, protein, and activity (20), whereas CYP2C11 protein and activity (but not mRNA) were increased at low viral doses. This demonstration of differential CYP regulation has implications not only for clinical adenoviral infections, but also for experimental use of adenoviral vectors to study CYP regulation and function.

Inflammatory bowel disease (IBD) in humans (ulcerative colitis and Crohn's disease) is characterized by an exaggerated inflammatory response in the intestinal mucosa (21). More than one million people in North America are afflicted with IBD, but little is known about its impact on CYP function or expression in humans or in animals. Masubuchi and Horie studied the effect of an established model of IBD, 3% dextran sulfate sodium given in the drinking water for 7 days, on hepatic activities of CYP3A2, 2C11, 1A2, 2E1, and 2D2. All activities except CYP2D2 were downregulated by DSS treatment, and were selectively prevented by treatment with polymyxin B (3A2, 2E1) or metronidazole (3A2, 2C11, 2E1), indicating that endotoxins of commensal bacteria are likely involved in some of the effects (22). It is unclear whether these changes in CYP activity reflected changes in gene expression.

Humans

The potentially dramatic effects of a severe infection on human drug metabolism were illustrated in a recent study in which the clearance of antipyrine was reduced by up to threefold, and its half-life prolonged up to fivefold, in children with bacterial sepsis and multiple organ failure (23). Because antipyrine is cleared by several CYP enzymes, this suggests that multiple CYPs may be downregulated in patients with sepsis. Clinical data are now emerging that identify specific CYP-dependent activities that are downregulated in inflammation. CYP3A4 is a predominant enzyme in human liver, and is involved in the metabolism of approximately 40% of therapeutic agents (1). CYP3A4 activity, measured by the erythromycin breath test, was reduced by 20%–60% following elective surgery in 16 patients (24). Similarly, an earlier study found that plasma levels of cyclosporine, a CYP3A4 substrate, were elevated in six patients following allogeneic bone marrow transplantation (25). Peak plasma levels of interleukin (IL)6 tended to precede the elevated cyclosporine levels by approximately 2 days. Together, these studies suggest that an inflammatory reaction contributes to decreased clearance of CYP3A4 substrates following surgery, but as discussed in Reference 24, other factors such as anesthetics, stress hormones, and altered hepatic blood flow could also contribute.

In patients with hepatitis C–positive liver cirrhosis, the presence of *Helicobacter pylori* infection was correlated with a 60%–70% decrease in the formation of monoethylglycylxylidide from lidocaine (26), a reaction catalyzed by CYP1A2. The effect of this highly prevalent infection on drug metabolism and CYP expression in otherwise healthy individuals remains to be determined, but this study highlights the possibility for the interaction and/or synergistic effects of coexisting inflammatory or infectious diseases.

Clozapine is an atypical neuroleptic drug used in the treatment of schizophrenia. It is metabolized primarily by CYP1A2 and 3A4. Haack et al. (27) reported four cases, and cited another 10 cases, of elevated plasma clozapine concentrations associated with infection or an inflammatory reaction. Inflammation and plasma clozapine elevations, which reached the toxic range, sometimes occurred in the absence of a detectable infection, and the authors suggested that this could be due to an inflammatory or hypersensitivity reaction to the drug itself (27). More work is needed to investigate this interesting and important hypothesis.

Emerging evidence suggests that the above findings may also have relevance for other diseases that have an important inflammatory component. As reviewed recently (28), chronic inflammation is a common feature in patients with solid tumors, and numerous studies in animals and in humans have found reduced clearance or decreased hepatic microsomal metabolism of CYP substrates. In lung and breast cancer patients, clearance of the CYP3A substrate erythromycin was inversely correlated with plasma levels of the inflammatory acute-phase protein C-reactive protein and IL6 (29). Similarly, changes (mainly decreases) in CYP-associated hepatic drug clearance have been documented in animals and patients with chronic or end-stage renal disease (30). Specific rat liver CYP mRNAs and proteins (CYPs 2C11 and 3A, but not 1A2, 2C6, 2D1, or 2E1) are downregulated in a rat model of chronic renal disease (31). It is likely that chronic inflammation associated with kidney disease contributes to the regulation in animals and humans (30), but this remains to be established.

MECHANISMS OF CYP REGULATION

Roles and Sources of Cytokines

Regulation of hepatic CYP expression in inflammation and infection has been attributed to the effects of inflammatory cytokines IL1β, IL6, tumor necrosis factor alpha (TNFα), and interferons (IFN) α or γ. Cytokines administered in vivo or incubated with cultured hepatocytes have enzyme-selective effects on CYP expression (6–10), and cultured hepatocytes have served as good models for the in vivo effects of cytokines (6). Importantly, cytokine regulation of CYP expression is similar in rodent and human hepatocytes (6).

Three laboratories have employed mice with targeted deletions of the genes for cytokines or cytokine receptors to elucidate what cytokines are important for the in vivo downregulation of CYPs. Absence of the genes for IL6, IL1β or the p55

and p75 receptors for TNFα had no effects on the downregulation of several CYP genes in the bacterial LPS model (15, 32, 33). This may be explained by functional redundancy of the various cytokines released during LPS-induced inflammation (15). In contrast to the LPS model, IL6 gene deficiency blocked the suppression of CYP1A2, 2A5, and 3A11 in mice treated with turpentine (15), and of CYP3A11 and 2C29 in mice treated with tuberculosis vaccine (33). Deletion of IL1β had no effect on CYP3A11 or 2C29 downregulation in the latter model, whereas deletion of the p55 TNFα receptor had partial effects (33). These results demonstrate a clear in vivo role for IL6 (and perhaps also TNFα) in downregulation of specific CYP genes in non-LPS models of sterile inflammation, and indicate that different cytokines are important in different disease states. Support for the role of IL6 also comes from studies in rabbit hepatocytes cultured with sera from turpentine-treated rabbits or humans with an upper respiratory viral infection (URVI). Fractionation of these sera, and neutralization with cytokine antibodies indicated that IL6 is responsible for both the short-term inhibition of CYP1A-dependent activities (34), and later downregulation of CYP1A1, 1A2, and 3A6 proteins and mRNAs (35). The same approach revealed additional roles of IFNγ, IL1β and TNFα serum from humans with an URVI (34, 35).

The functional redundancy of cytokines in CYP regulation in the LPS model is likely explained by the activation of Kupffer cells, resulting in local high concentrations of multiple cytokines. In the acute LPS model of CYP downregulation, destruction of Kupffer cells with gadolinium chloride inhibited cytokine induction in mouse liver, and also attenuated the downregulation of CYP3A11 (36). The role of Kupffer cells in CYP regulation in other models of inflammation and infection has yet to be determined. The apparent dominant role of IL6 in other sterile models of systemic inflammation may reflect its generation at extrahepatic sites and circulation in the blood.

Cellular Signaling Pathways

There is some evidence that oxidative stress plays a role in CYP downregulation by LPS treatment. CYP3A11 downregulation by LPS in mouse liver was inhibited by treatment with antioxidants and by inhibitors of xanthine oxidase and NADPH oxidase (36, 37). The vitamin E analog Trolox inhibited the decrease in total hepatic CYP caused by cecal ligation and puncture (CLP) in rats, and differentially inhibited the decreases in hepatic CYP2B1, 1A2, and 2E1 activities (38). It is unclear whether the effects of the antioxidants are due to inhibition of oxidative signals in the Kupffer cells, the hepatocytes, or both.

Oxidative stress may also contribute to the early inhibition of CYP activity that is observed in the absence of changes in protein expression. Inhibition of CYP-dependent activities and reduction of total CYP content in rabbit hepatocytes incubated with inflammatory sera were associated with lipid peroxidation (39). Antioxidants attenuated, and inhibitors of catalase, superoxide dismutase, or glutathione peroxidase potentiated these effects (39).

The roles of protein kinases in CYP downregulation have received little attention. Levitchi et al. (40) found that inhibitors of Janus-associated kinases, double-stranded RNA-dependent kinases, protein kinase C, and p42/44 mitogen-activated kinases were each capable of partially blocking the inhibition of CYP-dependent activities and reduction of total P450 content in short-term cultures of rabbit hepatocytes. The exact relationships of these kinases in the signaling mechanism remains to be determined.

Transcriptional Regulation

In most cases, downregulation of CYP activities and protein levels are accompanied or preceded by decreases in the respective CYP mRNAs (6, 8). We demonstrated recently that the transcription of CYP2C11, 3A2, and 2E1 is suppressed to 20%, 30%, and 10% of control, respectively, within 1–2 h of LPS treatment in rats (41). The swiftness and magnitude of these effects suggest that transcriptional suppression is the primary mechanism for the decline of CYP mRNAs.

The mechanisms of transcriptional downregulation of CYPs are complex, varied, and interdependent. Different mechanisms are likely to pertain depending on the specific gene and inflammatory stimulus, and also on the time point in the response. Changes in activity or expression of hepatic transcription factors during an acute-phase response, mediated primarily by inflammatory cytokines, are well documented (42), and their roles in CYP downregulation have been the subject of recent investigation and reviews (6–10). It is important to distinguish between mechanisms governing downregulation of basal versus drug-inducible transcription because the dominant transcription factors are different in each case.

A novel mechanism for the downregulation of constitutive CYP3A4 in response to inflammatory events has been proposed involving the transcription factor CCAAT enhancer binding protein, C/EBPβ. Upon administration of LPS in mice, the mRNA levels of C/EBP α decrease, whereas C/EBPβ and γ mRNAs increase (43). Expression of a truncated form of C/EBPβ lacking transactivation activity (LIP) is increased in hepatocytes after treatment with LPS (44) or proinflammatory cytokines (45, 46). Jover et al. (46) showed that LIP antagonized transactivation of CYP3A4 by full-length C/EBPβ (LAP), and downregulation of CYP3A4 correlated with a sharp decrease in the LAP:LIP ratio. Martinez-Jimenez et al. (47) recently identified an enhancer site in the CYP3A4 gene, at which LAP binds and activates transcription, while LIP antagonizes LAP activity. Changes in the LAP:LIP ratio can influence the regulation of CYP3A4 by other well-characterized mechanisms such as rifampicin induction (47). It will be important to determine if the mechanisms described for CYP3A4 have relevance for regulation of other CYPs and DMEs. Recent work in our lab found that the different forms of C/EBPβ were not significantly affected in rat liver 1 h after LPS injection and therefore changes in the LAP:LIP ratio are likely not involved in the suppression of CYP3A2, 2C11, or 2E1 at this early time point (41).

The expression of CYP2A5, the mouse ortholog of CYP2A6, is suppressed in response to LPS or turpentine injection and is upregulated in various rodent models

of hepatitis. The mechanism of downregulation is not clearly understood, but it is not mimicked by IL1β or IL6 injection (48). Pitarque et al. found that an interaction between hepatocyte nuclear factor-4 (HNF-4) and C/EBPα caused increased transcription of CYP2A6, whereas LAP and LIP caused downregulation in human hepatoma cells (49). Overexpression of LIP caused a greater downregulation than LAP. It would be interesting to examine this mechanism in inflammatory regulation of CYP2A6.

Hepatocyte nuclear factors (HNFs) regulate the basal transcription of many CYP genes. Therefore, downregulation of HNF expression or activities could contribute to suppression of CYPs. Downregulation of HNF1α is responsible for decreases in albumin, α_1-microglobin (42), CYP27A (50), and the sodium-dependent bile acid transporter (ntcp) (51). The promoters of CYP2E1 (52) and CYP2C11 (53) are transactivated by HNF1α. Moreover, Roe et al. (54) observed that the DNA binding activity of HNF1 is greatly reduced only 1 h after LPS injection in liver. HNF3β has been implicated in changes in gene regulation during inflammation (42) and plays an important role in basal transcription of CYP2C11 (53). HNF4α is required for basal transcription of rat CYP3A2 and 3A1 (55). We found that the DNA binding activities of HNF1α, HNF3β, and HNF4α were all rapidly reduced in the LPS treated rat liver, with HNF4α displaying the largest decrease at 53% (41). However, the size of these changes suggested that the suppression of CYPs was probably due to combined effects of LPS on multiple HNFs.

Although transcriptional regulation has been studied extensively using reporter systems, little is known about in vivo regulation of transcription during inflammation. For example, we reported that the CYP2C11 promoter contained a low-affinity binding site for NF-κB (56), and its mutation abrogated suppression of a CYP2C11 reporter (56). However, studies using curcumin, an inhibitor of NF-κB activation, suggested that the in vivo suppression of CYP2C11 was not dependent on NF-κB activation (41). More studies are needed with more effective and specific inhibitors of NF-κB.

Several mechanisms for suppression of drug-inducible CYP expression have been described. Suppression by inflammatory stimuli of induced transcription of CYP1A1 and 1A2 is due to a mutually antagonistic interaction of the aryl hydrocarbon receptor with NF-κB (57). Roles for the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR) in downregulation of inducible CYP, DME, and transporter transcription have been proposed. Loss of CYP3A and CYP2B following LPS treatment is associated with repression of CAR, PXR, and their dimerization partner retinoid X receptor (RXR) (58–60). Downregulation of phenobarbital or bilirubin-induced expression of CYP2B6, CYP2C9, CYP3A4, GSTA1, GSTA2, UGT1A1, and multiple drug resistance associated protein 2 (Mrp2) by IL1 in human hepatocytes or HepG2 cells is due to downregulation of CAR, which mediates the induction of these genes (61). The CAR gene is positively regulated by glucocorticoids, and repression of CAR was demonstrated to involve interference of the NF-κB p65 RelA subunit with glucocorticoid receptor-mediated transactivation of the CAR gene (61).

Because of the reduction of mouse hepatic PXR and CYP3As following LPS treatment, it has been suggested that downregulation of PXR could be causative for downregulation of constitutive CYP expression (36, 59). However, Sachdeva et al. described the downregulation of CYP3As in livers of rats undergoing CLP in the absence of changes in PXR expression, nuclear translocation, or response to inducers (62). Much higher doses of LPS were required for downregulation of CYP3A than were required for downregulation of nuclear PXR in rat liver, and moderate doses of LPS actually increased nuclear PXR levels (62). Similarly, Kim et al. reported that the dose of LPS required for half-maximal suppression of SULT2A1 mRNA in mice was 500- to 100-fold lower than that required to downregulate the nuclear receptors PXR, FXR, and RXRα, and they concluded that other mechanisms are likely involved (63). To definitively address the role of PXR in downregulation of constitutive expression of CYPs, DMEs, and transporters, two groups studied the regulation of these genes in PXR-null mice treated with LPS. Teng & Piquette-Miller (64) found that LPS downregulation of mRNAs for the transporters bile salt export pump (Bsep), multiple drug resistance protein 1a (Mdr1a, p-glycoprotein), multidrug resistance associated protein 2 (Mrp2), Mrp3, sodium-taurocholate cotransporting polypeptide (Ntcp), organic anion transporting polypeptide 2 (Oatp2), and CYP3A11 was similar in LPS-treated wild-type and PXR-null mice. However, in LPS-treated PXR-null mice, the extent of Mrp2 suppression was significantly diminished. In IL6-treated mice the downregulation of Bsep, Mrp2, and CYP3A11 mRNAs observed in wild type were not seen in the null mice. Significantly lower levels of PXR mRNA and protein were detected in endotoxin- and IL6-treated wild-type mice. In a similar study, we found that downregulation of mRNA expression of CYP1A2, 2A5, 2C29, 2E1, and 3A11 in response to LPS was identical in control and PXR-null mice (11). Taken together, these data show that downregulation of PXR is not critical for downregulation of CYP expression in the LPS or CLP models of inflammation. However, downregulation of PXR does influence the constitutive expression of some hepatic transporters, depending on the inflammatory stimulus.

The peroxisome proliferator activated receptor-α (PPARα) mediates the induction of hepatic CYP4A and other genes by peroxisome proliferators (65). CYP4A enzymes are induced in livers and kidneys of rats treated with LPS (16), but suppressed in mouse liver. The inflammatory induction of CYP4As in kidney is PPARα-mediated, because PPARα-null mice lack the response. The induction in rat liver is also thought to be PPARα-dependent (66). We considered the possibility that PPARα could be involved in downregulation of CYP expression in inflammatory models. PPARα negatively regulates the human fibrinogen gene in both constitutive and inflammatory conditions (67). Therefore, we studied the downregulation of CYP expression in PPARα-null mice. We found similar downregulation of CYP1A2, 2A5, 2C29, 2E1, and 3A11 by LPS treatment in the livers of wild type and PPARα-null mice, demonstrating that PPARα does not play a significant part in the suppression of these CYPs in the LPS model (11).

Posttranscriptional Regulation

The kinetics of mRNA suppression suggest that inflammatory regulation may involve destabilization or stabilization of mRNA for some CYPs (6), and this remains an under-studied area. Hepatic inflammation is a common precursor to CYP2A5 (mouse) and 2A6 (human) induction (68). CYP2A6 mRNA is stabilized when its transcription is impaired (69) by a mechanism involving binding of heterogeneous nuclear ribonucleoprotein A1 to the 3'UTR of CYP2A5 or 2A6.

Nitric Oxide

In response to inflammatory stimulation, hepatic production of nitric oxide (NO) is greatly stimulated owing to induction of inducible nitric oxide synthase (NOS2). The role of NO in the regulation of hepatic CYP expression in inflammation has been the subject of some debate, and the reader is referred to previous reviews for a more comprehensive discussion (6–10). A large number of studies have now shown that the downregulation of the majority of hepatic, drug-metabolizing CYP proteins and mRNAs is not affected by deletion of the NOS2 gene or by inhibitors of NOS enzymes. Pharmacologically derived NO is capable of inhibiting CYP2D6 reporter gene transcription by regulating the activity of transcription factors, including HNF4 and NFκB (70). This may be due to cysteine-nitrosylation of the DNA binding domains of HNF4 and NFκB p50 (71). However, the physiological relevance of this work has yet to be established, as CYP2D6 regulation in inflammation has not been demonstrated.

One CYP subfamily that is regulated by physiologically derived NO is CYP2B. We described a rapid, NO-dependent loss of CYP2B1/2 protein in rat hepatocytes occurring at high LPS concentrations, whereas a slower NO-independent pathway suppressed CYP2B1 mRNA at lower LPS concentrations (72). CYP2B1 activity is inhibited by incubation with peroxynitrite in vitro (73). This is due to nitration of tyrosine 190 because the Y190A mutation abolished this effect (74). It remains to be determined whether the NO-mediated downregulation of CYP2B1 in vivo requires tyrosine nitration. Minamiyama et al. (75) and Vuppugalla and Mehvar (76, 77) failed to detect nitrated CYP enzymes in microsomes or isolated perfused rat liver treated with NO donors, but in these studies the expression of CYP2B enzymes was very low because the animals were not treated with inducers.

It has been proposed that CYP inhibition or downregulation by NO may be due to nitrosylation of one or more cysteine or tyrosine residues (75, 76). Careful studies in the isolated perfused rat liver model demonstrated the loss of CYP heme and CYP activities within 30–60 min of perfusion with NO donors (76, 77) in the absence of changes in CYP protein levels. Effects of NO on drug-metabolizing CYPs were seen in less than one hour and varied depending on the isoform involved. CYP2D1 activity was not affected by NO in these experiments, and it was suggested that

NO is unable to interact with CYP2D1 at key sites, possibly due to the lack of cysteine and/or tyrosine residues.

Phosphorylation

The activities of CYP2Bs and CYP2E1 are reduced by cAMP-dependent phosphorylation of the enzymes (78, 79). In the case of CYP2B1, phosphorylation led to enzyme inactivation in less than 4 min, but protein levels remained unchanged for 3 h. Phosphorylation of CYP2E1 may cause both a loss of enzyme activity and protein degradation (78, 79). The possible role of phosphorylation in inflammatory regulation of CYP expression and activity deserves further study. As noted above, various protein kinase inhibitors have been shown to attenuate the inhibition of CYP activities by inflammatory sera in rabbit hepatocytes (40).

ROLE OF CYPs IN THE INFLAMMATORY RESPONSE

A significant question is whether hepatic CYP downregulation is important in the elaboration or resolution of the inflammatory response (8). We and others have posited several plausible roles that regulation of CYP enzymes could play in the inflammatory response (8). First, CYP enzymes produce reactive oxygen species owing to uncoupled enzymatic turnover (80), and overexpression of CYPs can cause endoplasmic reticulum stress (81). Oxidative stress is a contributing factor to LPS-induced liver injury (82), and CYP enzymes could be downregulated to avoid contributing further to this stress. Second, epoxyeicosatrienoic acids (EETs) formed by CYPs of the CYP2C and CYP2J subfamilies (and others) have anti-inflammatory as well as vasodilatory properties (83). Thus, CYPs that generate EETs may be downregulated either to allow unimpeded execution of the inflammatory response and/or to combat the hypotension that is a major morbidity factor in septic shock.

Another reason why multiple CYPs are downregulated could be related to a role of heme in the acute-phase response. Induction of the acute-phase protein α2-macroglobulin in rats is inhibited under conditions of heme deficiency (including induction of CYPs with phenobarbital) and augmented under conditions of heme repletion (84). Thus, CYP downregulation could possibly augment the acute-phase response by increasing heme availability.

Theories to explain the downregulation of P450s have largely centered on possible advantages conferred to the host by such regulation. However, a live infection is a dynamic struggle between the infecting microbe and its host, and we should consider the possibility that the microbe could be modulating CYP activity for its own purposes. For example, P450s could be involved in the metabolism of small molecules involved in microbial pathogenicity or the microbes could have evolved the ability to downregulate P450 to control host factors.

Effect on Inflammatory Responses of Manipulating P450 Activities

Several laboratories have found that modulators of CYP activity can affect fever, cytokines, and other endpoints in response to inflammation. These data should be interpreted with caution for the following reasons: (*a*) CYP inhibitors or inducers could have effects on inflammation that are unrelated to their effects on P450s properties, and (*b*) the specificities of most of the "specific" inhibitors used for inhibition of rodent CYPs are unknown.

CYP inhibitors exacerbate, and CYP inducers attenuate, fever caused by inflammatory stimuli. Pretreatment of rats with econazole or clotrimazole potentiated and prolonged the fever induced by IL1 infusion (85). Clotrimazole is a relatively specific inhibitor of CYP3A1 and 3A2 in rat liver microsomes (86), and so this experiment may implicate CYP3A enzymes, although clotrimazole also induces multiple CYPs in mice and rats (87). Kozak et al. (88) found that the nonspecific CYP inhibitor SKF525A augmented fever produced by LPS, caused a two- to threefold potentiation of plasma IL6, but inhibited TNFα production. Clotrimazole also dose-dependently potentiated fever, and this was reversed by injection of indomethacin. Similar effects of SKF525A and clotrimazole pretreatment were shown in rats (89). The CYP inducers bezafibrate and DHEA reduced fever induced by i.p. injection of LPS in male rats (90). Furthermore, icv infusion of 11,12-EET also inhibited fever. Interpretation of these results is complicated by the fact that bezafibrate and DHEA are PPARα ligands, and activation of PPARα is antiinflammatory, independent of CYP induction (91).

Pretreatment of mice or rats with dexamethasone (DEX) (which induces CYP3As and CYP2Bs) increases the serum TNFα and NO responses to LPS (92, 93). These effects of DEX pretreatment are blocked by troleandomycin (TAO) (94), suggesting that the DEX potentiation effect may be via a CYP3A enzyme. In contrast, DEX pretreatment reduced the serum IL6 and IL1 responses to LPS by $\sim$50%. Pretreatment of mice with the other CYP inducers did not potentiate the serum TNFα response to LPS (95). Conversely, the nonspecific CYP inhibitors SKF525A and metyrapone suppressed the serum (and spleen) TNFα responses to LPS in intact or adrenalectomized mice (95) without affecting IL6.

1-aminobenzotriazole (ABT) is a nonspecific suicide inhibitor of CYP enzymes, and it is potentially a good tool to study the role of CYP enzymes in inflammation. ABT infusion caused a 90% loss of hepatic CYP in rats, and treatment of these animals with 200 mg/kg zymosan, a dose that by itself was not lethal, caused 58% mortality (96). Zymosan injection is a model of fungal sepsis. ABT treatment also increased mortality in rats subjected to CLP, a model of polybacterial sepsis (97), and potentiated by 30%–50% the increases in serum TNFα, IL1, and IL6 measured at 10 h after CLP. These two studies strongly suggest an important protective role for CYP enzymes in models of sepsis. However, it is possible that ABT could be having effects other than CYP inhibition, and more work is necessary to establish the specificity and mechanism of this effect.

Given the above findings, one might predict that treatment with a CYP inducer would be protective against inflammatory processes. On the contrary, treatment of rats with phenobarbital potentiated liver damage caused by high-dose LPS (98). The CYP inhibitors TAO and ketoconazole inhibited liver damage caused by LPS in the absence or presence of prior induction with phenobarbital. The authors attributed these effects to a role of CYP3A enzymes.

REGULATION OF OTHER DMEs

Flavin-Containing Monooxygenases

Microsomal FMOs metabolize a variety of nitrogen- and sulfur-containing chemicals (2). Hepatic FMO activity is decreased in humans and rats with inflammatory conditions such as acute hepatitis or chemically induced cirrhosis (99–101). Rat liver FMO1 mRNA and activity are suppressed after LPS treatment (102), which is reversed upon inhibition of NOS2. Thus, NO is postulated to mediate LPS-induced decreases in FMO (102). FMO1 mRNA levels in rat hepatocytes are decreased after treatment with an LPS-cytokine mixture through mRNA destabilization, rather than decreased transcription (103). Further studies have indicated that NO directly and reversibly inhibits human FMO3 by an S-nitrosylation mechanism (104).

Phase II Enzymes

There is relatively little information concerning regulation of Phase II enzymes during inflammation, and this area requires much more study to determine which isoforms are regulated by which inflammatory stimuli and the mechanisms involved.

UGTs are regulated by factors known to be affected by inflammation (see discussion above for CYPs), such as farnesoid X receptor (FXR), RXR, PPARα, and HNF4 (105–108). Minor decreases in hepatic UGT activities were reported after administration of LPS in rats and isolated perfused mouse liver (109, 110), but no effect on UGTs was observed in mouse hepatocytes (110) or after injection of individual cytokines in rats (109). In isolated pig hepatocytes (111), IL1α and TNFα caused early inhibition of glucuronidation. Hepatic microsomal glucuronidation of p-nitrophenol (UGT1A6) was unchanged in the livers of turpentine-treated rats, whereas activity (testosterone) and mRNA of UGT2B3 were decreased at 24 h (112). IL6, but not IL1β, suppressed UGT1A1 and 2B3 mRNA expression in isolated rat hepatocytes (112). In LNCaP prostate cancer cell lines, 6 days of IL1α treatment suppressed testosterone glucuronidation by 70%, and specifically suppressed the mRNA and protein of UGT2B17, but not UGT2B15 (113). Luciferase reporter assays localized the IL1 response to the proximal 267 bp of the UGT2B17 promoter. In a single study with human liver biopsies, Congiu et al. (114) correlated decreased UGT1A4, 2B4, and 2B7 mRNA levels with increased inflammation.

SULT enzymes catalyze the transfer of sulfate from 3′-phosphoadenosine 5′-phosphosulfate (PAPS) to molecules, increasing their water solubility (4). Cholesterol and its derivatives, bile acids, and steroids undergo sulfonation as part of their normal metabolism. As such, downregulation of SULT enzymes may be important in LPS-induced cholestasis. In particular, SULT2A1 catalyzes the sulfonation of the toxic bile acid lithocholic acid (115) and of the sex steroid dehydroepiandrosterone (DHEA). Kim et al. (63) demonstrated that levels of SULT2A1 mRNA, PAPS synthase 2, and SULT2A1 protein activity are dramatically decreased in mouse liver after very low doses of LPS. Shimada et al. (116) observed downregulation of rat SULT1A1 and 1C1 mRNA, proteins, and activities after LPS treatment as early as 6 h, with 63% and 76% suppression of sulfating activity for p-nitrophenol and *N*-hydroxy-2-acetylaminofluorene. Pretreatment of rats with dexamethasone (DEX) prevented the suppression of SULT1A1 and 1B1 mRNAs by LPS, whereas treatment of HepG2 cells with IL6 decreased SULT proteins (116). Additionally, TNFα and IL1β caused a significant decrease in the mRNA levels of human SULT2A1 in Hep 3B hepatoma cells, consistent with earlier findings of cytokine-mediated inhibition of nuclear receptor mRNAs and proteins (60).

There are several possible mechanisms for downregulation of SULTs during LPS-induced inflammation. Transcription of SULT2A1 is regulated by FXR, CAR, PXR, and RXR, each of which is suppressed during inflammation (58–60). Altered activity of FXR/RXR, CAR/RXR, and/or PXR/RXR could lead to changes in the mRNA levels of SULT2A1 and PAPSS2, ultimately regulating the metabolism of hydroxysteroids and bile acids. Transcription factors (TF) other than nuclear receptors may also regulate SULT2A1, including HNF1 and C/EBP. Song et al. (117) showed two HNF1 and three C/EBP response elements in the rat SULT2A1 promoter, as well as evidence for HNF4 or liver receptor homolog-1 (LRH-1) response elements.

GST proteins catalyze the conjugation of electrophilic chemicals or metabolites with glutathione (5). Maheo et al. (118) found no effect on constitutive hepatic GST mRNA expression or protein activity toward 1-chloro-2, 4-dinitrobenzene in the rat after 1 mg/kg LPS treatment at either 6 or 24 h. However, LPS inhibited the induction of GSTA1/2, M1, and P1 mRNAs by oltipraz at 24 h. Other studies showed differential effects on basal GST isozyme expression after in vivo LPS administration. rGSTA2 and A3 were significantly suppressed, whereas rGSTM1 and M2 were less affected (119, 120). LPS downregulated allyl disulfide- and oltipraz-inducible expression of rGSTA2, A3, M1, and M2 mRNAs in rat liver by 50%–90% (119). Mechanisms for downregulation of GST mRNAs during inflammation are being elucidated. Maheo et al. (121) found that IL1β suppressed rGSTA2 and M1 mRNAs in rat hepatocytes, but induced rGSTP1 at later times. The decline in rGSTM1 mRNA was not due to decreased transcription, but rather to accelerated degradation of the mRNA (121). IL6, in the presence of dexamethasone (DEX), downregulates expression of rat GSTA2 in rat hepatocytes (122). Voss et al. (123) found a novel nuclear protein induced by both IL6 and DEX (IL6DEX-NP) that binds to a promoter element adjacent to the HNF1 site of rGSTA2 and

decreases its expression. Based on the kinetics of rGSTA2 gene expression and of DNA binding activity of IL6DEX-NP and HNF1 to an rGSTA2 promoter probe, it was concluded that early decreases in rGSTA2 after LPS are due to decreased binding of HNF1, and later decreases in transcriptional rate are due to increased IL6DEX-NP binding (124).

REGULATION OF HEPATIC TRANSPORTERS

Human and rodent hepatic transport systems have an integral function in drug metabolism and disposition, and have been reviewed thoroughly (125). Efflux proteins, such as p-glycoprotein (Mdr1a, Pgp) and Mrp 2, can be coordinately regulated with CYP, UGT, and GST enzymes. For example, known CYP3A4 substrates cyclosporin A and saquinavir have <50% oral bioavailability, which reflects both CYP3A4 metabolism and Pgp excretion (125, 126). Development and investigation of mdr1a-null mice indicated that null mice are 50- to 100-fold more sensitive to toxicity caused by the pesticide ivermectin, an mdr1a substrate (125, 127, 128).

Cholestasis can occur in response to a variety of inflammatory stimuli (129), and LPS-mediated cholestasis is a result of altered expression and activity of hepatic transporters. In vitro and in vivo studies in rats indicate that LPS, TNFα, IL1β, or IL6 decreases the uptake and secretion of bile components (130–132). Organic anions are taken up from the blood by the Ntcp transporter and organic anion transporting polypeptides (Oatp), whereas organic anions are secreted into the bile by Bsep and Mrp2. Mrp3 and 4 are induced during cholestasis to transport toxic bile acids back into the blood (133, 134).

Numerous studies indicate that exposure to inflammatory stimuli such as LPS and turpentine decrease mRNA levels of hepatic transporters in rats and mice (Table 1). LPS produces dramatic decreases in the mRNA levels of rat and human Ntcp; Bsep; Oatps 1, 2, and 4; Mrp2, Mrp3 (135–145), as well as mouse mdr1a, mdr1b, mdr2, and sister p-glycoprotein (spgp) (146–150). Some reports indicate that LPS does not affect Mrp1 (139), whereas others demonstrate upregulation of Mrp1 (136, 142), as well as Mdr1b (136), Mrp5, and Mrp6 (151) after LPS treatment.

In an extensive study, Cherrington et al. (142) found decreased rat hepatic mRNA levels of 10 different transporters 6 h after LPS administration, including Mrp2 and Mrp6, but no changes in Mrp5 expression. LPS increased Mrp1, Mrp3, and Mdr1b mRNA expression (142). On the contrary, Donner et al. (151) found upregulation of Mrp5 and 6 after LPS treatment. Interestingly, pretreatment with aminoguanidine or gadolinium chloride had no effect on the LPS-induced changes in transporter levels (142), suggesting that neither NO nor Kupffer cells play important roles.

A number of studies suggest that cytokines are significantly involved in transporter downregulation. Administration of IL1β, IL6, or TNFα decreases rodent

TABLE 1 Regulation of rodent hepatic basolateral and canalicular transporters during inflammation

Transporter[a]	Stimulus	Regulation	References
Ntcp[a]	LPS	↓	(64, 141, 142, 144, 154)
	Turpentine	↓	(154)
Bsep	LPS	↓	(65, 142–144, 154)
	Turpentine	↓	(139, 154)
Oatp1	LPS	↓	(139, 141, 142, 154)
	Turpentine	↓	(154)
Oatp2	LPS	↓	(64, 139, 141, 142)
Oatp4	LPS	↓	(142, 153)
Oat2	LPS	↔	(142)
Oat3	LPS	↓	(142)
Oct1	LPS	↓	(142)
Mrp1	LPS	↑ or ↔	(136, 139, 142)
Mrp2	LPS	↓	(64, 136, 137, 138, 139, 141, 142, 144, 151, 154)
	Turpentine	↓	(154)
Mrp3	LPS	↓ or ↑	(64, 139, 142, 154)
	Turpentine	↓	(154)
Mrp4	LPS	↔	(151)
Mrp5	LPS	↑ or ↔	(142, 151)
Mrp6	LPS	↑ or ↓	(142, 151)
Mdr1a	LPS	or ↔	(64, 142, 146, 148, 149)
	Turpentine	↓	(146–148)
Mdr1b	LPS	↓ or ↔ or ↑	(64, 136, 142, 148)
	Turpentine	↓	(147, 148)
Mdr2	LPS	↓	(64, 148)
	Turpentine	↓	(148)
Spgp	LPS	↓	(136, 148)

[a]Ntcp, Na-taurocholate cotransporting polypeptide; Bsep, bile salt export protein; Oatp, organic anion transporting polypeptide; Oat, organic anion transporter; Oct, organic cation transporter; Mrp, multidrug resistance associated protein; Mdr, multidrug resistance protein; spgp; sister of p-glycoprotein.

hepatic mRNA levels of Ntcp, Bsep, Oatp1 and 2, Mrp 2 and 3, Mdr1a, 1b, and 2, as well as spgp. Hartmann et al. (139) found that IL6 or IL1 administration suppressed Mrp2, Oatp1, Oatp2, and Bsep mRNA levels to 20%–60% of controls. TNFα administration affected mRNA levels of Mrp2, Mrp3, and Oatp2, but not Oatp1 or Bsep (139). In human HuH7 cells, IL1β, IL6, and TNFα decreased MDR1 mRNA and MDR1-mediated efflux of Rhodamine-123, but only TNFα

decreased MDR1 in HepG2 cells (152). IL1β and IL6 treatment also increased human MRP1 in HepG2 cells (152).

Studies of Oatp4 mRNA regulation indicated similar LPS downregulation of Oatp4 in wild-type mice and mice lacking TNF receptor p55, IL1 receptor, IL6, and iNOS over a 48 h time period (153). These findings are reminiscent of those described above for CYP regulation in the LPS model. Furthermore, Siewert et al. (154) compared responses in IL6 wild-type and null mice after LPS, turpentine, and IL6 injection. Downregulation of Ntcp, Bsep, Oatp1, Mrp2, and Mrp3 mRNAs occurred after each treatment. In IL6-null mice, turpentine failed to decrease transporter mRNA levels, again similar to regulation of CYPs in the turpentine model (15). However, LPS-mediated downregulation of Ntcp, Mrp3, and Mrp2 was also abolished in the IL6-null mice at 24 h, in contrast to CYP regulation by LPS. It was concluded that IL6 is required for transporter downregulation during turpentine-induced inflammation and contributes to regulation during LPS-induced cholestasis at delayed time points (154). Miyoshi et al. (150) found that LPS failed to downregulate hepatic Pgp mRNA levels at 6 or 24 h after LPS treatment in TNFα-null mice, suggesting that TNFα has a pivotal role in Pgp downregulation by LPS.

Induction of Mdr1b expression in rat hepatocytes occurs via a NF-κB-dependent mechanism (155). As noted above, Trauner et al. (51) found that downregulation of HNF1 (44% of pretreatment levels) is partially responsible for suppression of the Ntcp promoter after LPS administration. Other studies of Ntcp indicate that LPS treatment of rats and IL1β treatment of HepG2 cells decreases the binding activity of the heterodimer RXR/RAR (retinoic acid receptor) (156). Teng & Piquette-Miller (64) studied the role of PXR in downregulation of hepatic Bsep, Mdr1a, Mrp2, Mrp3, and Oatp2 after LPS treatment. Downregulation of Mrp2 was attenuated in PXR KO mice, whereas the downregulation of the other transporters showed no evidence of a requirement for PXR.

SUMMARY

The regulation of Phase II enzymes and transporters in inflammation exhibit many similarities with CYP regulation, but also some significant differences. We are only beginning to understand the complex mechanisms involved in this regulation. Studies in which CYP activity is modulated reveal significant effects on the inflammatory response, suggesting that regulation of CYPs may be involved in homeostatic or pathophysiological responses. However, the results are sometimes contradictory, and more work is needed in this area. Studies to date using aseptic models of inflammation have yielded much information, but more data are needed from other models, especially live models of infection, to understand how different infective agents can differentially regulate DMEs and transporters in vivo. Clinical data on the effects of infection and inflammation on CYPs and enzymes remain scarce, and again more studies are needed to understand how human drug

disposition is regulated in diseases that have inflammation either as a primary or a secondary component.

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LITERATURE CITED

1. Guengerich FP. 2003. Cytochromes P450, drugs and diseases. *Mol. Interv.* 3:194–202
2. Cashman J. 2003. The role of flavin-containing monooxygenases in drug metabolism and development. *Curr. Opin. Drug Discov. Dev.* 6:486–93
3. Mackenzie PI, Gregory PA, Gardner-Stephen DA, Lewinsky RH, Jorgensen BR, et al. 2003. Regulation of UDP glucuronosyltransferase genes. *Curr. Drug Metab.* 4:249–57
4. Coughtrie MW. 2002. Sulfation through the looking glass—recent advances in sulfotransferase research for the curious. *Pharmacogenomics J.* 2:297–308
5. Hayes JD, Flanagan JU, Jowsey IR. 2005. Glutathione transferases. *Annu. Rev. Pharmacol. Toxicol.* 45:51–88
6. Morgan ET. 1997. Regulation of cytochromes P450 during inflammation and infection. *Drug Metab. Rev.* 29:1129–88
7. Renton KW. 2000. Hepatic drug metabolism and immunostimulation. *Toxicology* 142:173–78
8. Morgan ET. 2001. Regulation of cytochrome P450 by inflammatory mediators: why and how? *Drug Metab. Dispos.* 29:207–12
9. Renton KW. 2001. Alteration of drug biotransformation and elimination during infection and inflammation. *Pharmacol. Ther.* 92:147–63
10. Renton KW. 2004. Cytochrome P450 regulation and drug biotransformation during inflammation and infection. *Curr. Drug Metab.* 5:235–43
11. Richardson TA, Morgan ET. 2005. Hepatic cytochrome P450 gene regulation during endotoxin-induced inflammation in nuclear receptor knockout mice. *J. Pharmacol. Exp. Ther.* 314:703–9
12. Sewer MB, Koop DR, Morgan ET. 1996. Endotoxemia in rats is associated with induction of the P4504A subfamily and suppression of several other forms of cytochrome P450. *Drug Metab. Dispos.* 24: 401–7
13. Barclay TB, Peters JM, Sewer MB, Ferrari L, Gonzalez FJ, Morgan ET. 1999. Modulation of cytochrome P-450 gene expression in endotoxemic mice is tissue specific and peroxisome proliferator-activated receptor-alpha dependent. *J. Pharmacol. Exp. Ther.* 290:1250–57
14. Fang C, Yoon SJ, Tindberg N, Järveläinen HA, Lindros KO, Ingelman-Sundberg M. 2004. Hepatic expression of multiple acute phase proteins and down-regulation of nuclear receptors after acute endotoxin exposure. *Biochem. Pharmacol.* 67:1389–97
15. Siewert E, Bort R, Kluge R, Heinrich PC, Castell J, Jover R. 2000. Hepatic cytochrome P450 down-regulation during aseptic inflammation in the mouse is interleukin 6 dependent. *Hepatology* 32:49–55

16. Sewer MB, Koop DR, Morgan ET. 1997. Differential inductive and suppressive effects of endotoxin and particulate irritants on hepatic and renal cytochrome P-450 expression. *J. Pharmacol. Exp. Ther.* 280: 1445–54
17. Iber H, Sewer MB, Barclay TB, Mitchell SR, Li T, Morgan ET. 1999. Modulation of drug metabolism in infectious and inflammatory diseases. *Drug Metab. Rev.* 31:29–41
18. Shimamoto Y, Kitamura H, Iwai M, Saito M, Kazusaka A, Fujita S. 1999. Mechanism of decrease in levels of hepatic P450 isozymes induced by intracerebral endotoxin: independence from sympathetic nervous and adrenocortical systems. *Arch. Toxicol.* 73:41–49
19. Goralski KB, Abdulla C, Sinal CJ, Arsenault A, Renton KW. 2005. Toll-like receptor-4 regulation of hepatic Cyp3a11-metabolism in a mouse model of LPS induced CNS inflammation. *Am. J. Physiol. Gastrointest. Liver Physiol.* 289:G434–43
20. Callahan SM, Ming X, Lu SK, Brunner LJ, Croyle MA. 2005. Considerations for use of recombinant adenoviral vectors: dose effect on hepatic cytochromes P450. *J. Pharmacol. Exp. Ther.* 312:492–501
21. Caradonna L, Amati L, Magrone T, Pellegrino NM, Jirillo E, Caccavo D. 2000. Enteric bacteria, lipopolysaccharides and related cytokines in inflammatory bowel disease: biological and clinical significance. *J. Endotoxin Res.* 6:205–14
22. Masubuchi Y, Horie T. 2004. Endotoxin-mediated disturbance of hepatic cytochrome P450 function and development of endotoxin tolerance in the rat model of dextran sulfate sodium-induced experimental colitis. *Drug Metab. Dispos.* 32: 437–41
23. Carcillo JA, Doughty L, Kofos D, Frye RF, Kaplan SS, et al. 2003. Cytochrome P450 mediated-drug metabolism is reduced in children with sepsis-induced multiple organ failure. *Intensive Care Med.* 29:980–84
24. Haas CE, Kaufman DC, Jones CE, Burstein AH, Reiss W. 2003. Cytochrome P450 3A4 activity after surgical stress. *Crit. Care Med.* 31:1338–46
25. Chen YL, Le Vraux V, Leneveu A, Dreyfus F, Stheneur A, et al. 1994. Acute-phase response, interleukin-6, and alteration of cyclosporine pharmacokinetics. *Clin. Pharmacol. Ther.* 55:649–60
26. Giannini E, Fasoli A, Botta F, Romagnoli P, Malfatti F, et al. 2003. Helicobacter pylori infection is associated with greater impairment of cytochrome P-450 liver metabolic activity in anti-HCV positive cirrhotic patients. *Dig. Dis. Sci.* 48:802–8
27. Haack MJ, Bak ML, Beurskens R, Maes M, Stolk LM, Delespaul PA. 2003. Toxic rise of clozapine plasma concentrations in relation to inflammation. *Eur. Neuropsychopharmacol.* 13:381–85
28. Slaviero KA, Clarke SJ, Rivory LP. 2003. Inflammatory response: an unrecognised source of variability in the pharmacokinetics and pharmacodynamics of cancer chemotherapy. *Lancet Oncol.* 4:224–32
29. Rivory LP, Slaviero KA, Clarke SJ. 2002. Hepatic cytochrome P450 3A drug metabolism is reduced in cancer patients who have an acute-phase response. *Br. J. Cancer* 87:277–80
30. Nolin TD, Frye RF, Matzke GR. 2003. Hepatic drug metabolism and transport in patients with kidney disease. *Am. J. Kidney Dis.* 42:906–25
31. Leblond F, Guevin C, Demers C, Pellerin I, Gascon-Barre M, Pichette V. 2001. Downregulation of hepatic cytochrome P450 in chronic renal failure. *J. Am. Soc. Nephrol.* 12:326–32
32. Warren GW, Poloyac SM, Gary DS, Mattson MP, Blouin RA. 1999. Hepatic cytochrome P-450 expression in tumor necrosis factor-a receptor (p55/p75) knockout mice after endotoxin administration. *J. Pharmacol. Exp. Ther.* 288: 945–50
33. Ashino T, Oguro T, Shioda S, Horai R, Asano M, et al. 2004. Involvement

of interleukin-6 and tumor necrosis factor alpha in CYP3A11 and 2C29 downregulation by Bacillus Calmette-Guerin and lipopolysaccharide in mouse liver. *Drug Metab. Dispos.* 32:707–14

34. Bleau AM, Levitchi MC, Maurice H, Du Souich P. 2000. Cytochrome P450 inactivation by serum from humans with a viral infection and serum from rabbits with a turpentine-induced inflammation: the role of cytokines. *Br. J. Pharmacol.* 130:1777–84
35. Bleau AM, Maurel P, Pichette V, Leblond F, Du Souich P. 2003. Interleukin-1beta, interleukin-6, tumour necrosis factor-alpha and interferon-gamma released by a viral infection and an aseptic inflammation reduce CYP1A1, 1A2 and 3A6 expression in rabbit hepatocytes. *Eur. J. Pharmacol.* 473:197–206
36. Xu DX, Wei W, Sun MF, Wu CY, Wang JP, et al. 2004. 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.* 37:10–22
37. Xu DX, Wei W, Sun MF, Wei LZ, Wang JP. 2005. Melatonin attenuates lipopolysaccharide-induced downregulation of pregnane X receptor and its target gene CYP3A in mouse liver. *J. Pineal Res.* 38:27–34
38. Park SW, Lee SM. 2004. The beneficial effect of Trolox on sepsis-induced hepatic drug metabolizing dysfunction. *Arch. Pharm. Res.* 27:232–38
39. El-Kadi AO, Bleau AM, Dumont I, Maurice H, du Souich P. 2000. Role of reactive oxygen intermediates in the decrease of hepatic cytochrome P450 activity by serum of humans and rabbits with an acute inflammatory reaction. *Drug Metab. Dispos.* 28:1112–20
40. Levitchi M, Fradette C, Bleau AM, Michaud D, Kourylko O, et al. 2004. Signal transduction pathways implicated in the decrease in CYP1A1, 1A2 and 3A6 activity produced by serum from rabbits and humans with an inflammatory reaction. *Biochem. Pharmacol.* 68:573–82
41. Cheng PY, Wang ML, Morgan ET. 2003. Rapid transcriptional suppression of rat cytochrome P450 genes by endotoxin treatment and its inhibition by curcumin. *J. Pharmacol. Exp. Ther.* 307:1205–12
42. Ruminy P, Gangneux C, Claeyssens S, Scotte M, Daveau M, Salier JP. 2001. Gene transcription in hepatocytes during the acute phase of a systemic inflammation: from transcription factors to target genes. *Inflamm. Res.* 50:383–90
43. Cantwell CA, Sterneck E, Johnson PF. 1998. Interleukin-6-specific activation of the C/EBPdelta gene in hepatocytes is mediated by Stat3 and Sp1. *Mol. Cell. Biol.* 18:2108–17
44. An MR, Hsieh CC, Reisner PD, Rabek JP, Scott SG, et al. 1996. Evidence for post-transcriptional regulation of C/EBPalpha and C/EBPbeta isoform expression during the lipopolysaccharide-mediated acute-phase response. *Mol. Cell. Biol.* 16:2295–306
45. Baumann H, Morella KK, Campos SP, Cao Z, Jahreis GP. 1992. Role of CAAT-enhancer binding protein isoforms in the cytokine regulation of acute-phase plasma protein genes. *J. Biol. Chem.* 267:19744–51
46. Jover R, Bort R, Gómez-Lechón MJ, Castell JV. 2002. Down-regulation of human CYP3A4 by the inflammatory signal interleukin 6: molecular mechanism and transcription factors involved. *FASEB J.* 16:1799–801
47. Martinez-Jimenez CP, Gomez-Lechon MJ, Castell JV, Jover R. 2005. Transcriptional regulation of the human hepatic CYP3A4: Identification of a new distal enhancer region responsive to CCAAT/enhancer binding protein beta isoforms (LAP and LIP). *Mol. Pharmacol.* 67: 2088–101
48. Gilmore WJ, Hartmann G, Piquette-Miller M, Marriott J, Kirby GM. 2003.

Effects of lipopolysaccharide-stimulated inflammation and pyrazole-mediate d hepatocellular injury on mouse hepatic Cyp2a5 expression. *Toxicology* 184:211–26

49. Pitarque M, Rodriguez-Antona C, Oscarson M, Ingelman-Sundberg M. 2005. Transcriptional regulation of the human CYP2A6 gene. *J. Pharmacol. Exp. Ther.* 313:814–22
50. Memon RA, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. 2001. In vivo and in vitro regulation of sterol 27-hydroxylase in the liver during the acute phase response. Potential role of hepatocyte nuclear factor-1. *J. Biol. Chem.* 276: 30118–26
51. Trauner M, Arrese M, Lee H, Boyer JL, Karpen SJ. 1998. Endotoxin downregulates rat hepatic ntcp gene expression via decreased activity of critical transcription factors. *J. Clin. Invest.* 101:2092–100
52. McGehee RE Jr, Ronis MJJ, Badger TM. 1997. Regulation of the hepatic CYP 2E1 gene during chronic alcohol exposure: lack of an ethanol response element in the proximal 5′-flanking sequence. *DNA Cell Biol.* 16:725–36
53. Park SH, Waxman DJ. 2001. Inhibitory cross-talk between STAT5b and liver nuclear factor HNF3beta—impact on the regulation of growth hormone pulse-stimulated, male-specific liver cytochrome P-450 gene expression. *J. Biol. Chem.* 276:43031–39
54. Roe AL, Poloyac SM, Howard G, Shedlofsky SI, Blouin RA. 2001. The effect of endotoxin on hepatocyte nuclear factor 1 nuclear protein binding: potential implications on CYP2E1 expression in the rat. *J. Pharm. Pharmacol.* 53:1365–71
55. Ogino M, Nagata K, Miyata M, Yamazoe Y. 1999. Hepatocyte nuclear factor 4-mediated activation of rat CYP3A1 gene and its modes of modulation by apolipoprotein AI regulatory protein I and v-ErbA-related protein 3. *Arch. Biochem. Biophys.* 362:32–37
56. Iber H, Chen Q, Cheng P-Y, Morgan ET. 2000. Suppression of CYP2C11 gene transcription by interleukin-1 mediated by NF-kB binding at the transcription start site. *Arch. Biochem. Biophys.* 377:187–94
57. Ke S, Rabson AB, Germino JF, Gallo MA, Tian Y. 2001. Mechanism of suppression of cytochrome P-450 1A1 expression by tumor necrosis factor-alpha and lipopolysaccharide. *J. Biol. Chem.* 276: 39638–44
58. Beigneux AP, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. 2000. The acute phase response is associated with retinoid X receptor repression in rodent liver. *J. Biol. Chem.* 275:16390–99
59. Beigneux AP, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. 2002. 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.* 293: 145–49
60. Kim MS, Shigenaga J, Moser A, Feingold K, Grunfeld C. 2003. Repression of farnesoid X receptor during the acute phase response. *J. Biol. Chem.* 278:8988–95
61. Assenat E, Gerbal-Chaloin S, Larrey D, Saric J, Fabre JM, et al. 2004. Interleukin 1beta inhibits CAR-induced expression of hepatic genes involved in drug and bilirubin clearance. *Hepatology* 40:951–60
62. Sachdeva K, Yan B, Chichester CO. 2003. Lipopolysaccharide and cecal ligation/puncture differentially affect the subcellular distribution of the pregnane X receptor but consistently cause suppression of its target genes CYP3A. *Shock* 19:469–74
63. Kim MS, Shigenaga J, Moser A, Grunfeld C, Feingold KR. 2004. Suppression of DHEA sulfotransferase (Sult2A1) during the acute-phase response. *Am. J. Physiol. Endocrinol. Metab.* 287:E731–38

64. Teng S, Piquette-Miller M. 2005. The involvement of the pregnane X receptor in hepatic gene regulation during inflammation in mice. *J. Pharmacol. Exp. Ther.* 312:841–48
65. Johnson EF, Palmer CNA, Griffin KJ, Hsu MH. 1996. Cytochromes P450.7. Role of the peroxisome proliferator-activated receptor in cytochrome P450 4A gene regulation. *FASEB J.* 10:1241–48
66. Mitchell SR, Sewer MB, Kardar SS, Morgan ET. 2001. Characterization of CYP4A induction in rat liver by inflammatory stimuli: dependence on sex, strain, and inflammation-evoked hypophagia. *Drug Metab. Dispos.* 29:17–22
67. Gervois P, Vu-Dac N, Kleemann R, Kockx M, Dubois G, et al. 2001. Negative regulation of human fibrinogen gene expression by peroxisome proliferator-activated receptor alpha agonists via inhibition of CCAAT box/enhancer-binding protein beta. *J. Biol. Chem.* 276:33471–77
68. Su T, Ding X. 2004. Regulation of the cytochrome P450 2A genes. *Toxicol. Appl. Pharmacol.* 199:285–94
69. Christian K, Lang M, Maurel P, Raffalli-Mathieu F. 2004. Interaction of heterogeneous nuclear ribonucleoprotein A1 with cytochrome P450 2A6 mRNA: implications for post-transcriptional regulation of the CYP2A6 gene. *Mol. Pharmacol.* 65: 1405–14
70. Hara H, Adachi T. 2002. Contribution of hepatocyte nuclear factor-4 to down-regulation of CYP2D6 gene expression by nitric oxide. *Mol. Pharmacol.* 61:194–200
71. Vossen C, Erard M. 2002. Down-regulation of nuclear receptor DNA-binding activity by nitric oxide—HNF4 as a model system. *Med. Sci. Monit.* 8:RA217–20
72. Ferrari L, Peng N, Halpert JR, Morgan ET. 2001. Role of nitric oxide in down-regulation of CYP2B1 protein, but not RNA, in primary cultures of rat hepatocytes. *Mol. Pharmacol.* 60:209–16
73. Roberts ES, Lin H, Crowley JR, Vuletich JL, Osawa Y, Hollenberg PF. 1998. Peroxynitrite-mediated nitration of tyrosine and inactivation of the catalytic activity of cytochrome P450 2B1. *Chem. Res. Toxicol.* 11:1067–74
74. Lin HL, Kent UM, Zhang H, Waskell L, Hollenberg PF. 2003. Mutation of tyrosine 190 to alanine eliminates the inactivation of cytochrome P450 2B1 by peroxynitrite. *Chem. Res. Toxicol.* 16: 129–36
75. Minamiyama Y, Takemura S, Imaoka S, Funae Y, Tanimoto Y, Inoue M. 1997. Irreversible inhibition of cytochrome P450 by nitric oxide. *J. Pharmacol. Exp. Ther.* 283:1479–85
76. Vuppugalla R, Mehvar R. 2004. Short-term inhibitory effects of nitric oxide on cytochrome P450-mediated drug metabolism: time dependency and reversibility profiles in isolated perfused rat livers. *Drug Metab. Dispos.* 32:1446–54
77. Vuppugalla R, Mehvar R. 2004. Hepatic disposition and effects of nitric oxide donors: rapid and concentration-dependent reduction in the cytochrome P450-mediated drug metabolism in isolated perfused rat livers. *J. Pharmacol. Exp. Ther.* 310:718–27
78. Oesch-Bartlomowicz B, Oesch F. 2003. Cytochrome-P450 phosphorylation as a functional switch. *Arch. Biochem. Biophys.* 409:228–34
79. Oesch-Bartlomowicz B, Oesch F. 2002. Fast regulation of cytochrome P450 activities by phosphorylation and consequences for drug metabolism and toxicity. *Biol. Chem.* 383:1587–92
80. White RE, Coon MJ. 1980. Oxygen activation by cytochrome P-450. *Annu. Rev. Biochem.* 49:315–56
81. Szczesna-Skorupa E, Chen CD, Liu H, Kemper B. 2004. Gene expression changes associated with the endoplasmic reticulum stress response induced by microsomal cytochrome P450 overproduction. *J. Biol. Chem.* 279:13953–61

82. Balk RA. 2000. Pathogenesis and management of multiple organ dysfunction or failure in severe sepsis and septic shock. *Crit. Care Clin.* 16:337–52, vii
83. Fleming I. 2001. Cytochrome P450 enzymes in vascular homeostasis. *Circ. Res.* 89:753–62
84. Lyoumi S, Puy H, Tamion F, Bogard C, Leplingard A, et al. 1999. Heme and acute inflammation—role in vivo of heme in the hepatic expression of positive acute-phase reactants in rats. *Eur. J. Biochem.* 261: 190–96
85. Nakashima T, Harada Y, Miyata S, Kiyohara T. 1996. Inhibitors of cytochrome P-450 augment fever induced by interleukin-1 beta. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 271:R1274–79
86. Turan VK, Mishin VM, Thomas PE. 2001. Clotrimazole is a selective and potent inhibitor of rat cytochrome P450 3A subfamily-related testosterone metabolism. *Drug Metab. Dispos.* 29:837–42
87. Pappas JB, Franklin MR. 1993. Hepatic clotrimazole concentrations and hepatic drug metabolizing enzyme activities in adult male Sprague-Dawley rats. *Toxicology* 80:27–35
88. Kozak W, Archuleta I, Mayfield KP, Kozak A, Rudolph K, Kluger MJ. 1998. Inhibitors of alternative pathways of arachidonate metabolism differentially affect fever in mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 275:R1031–40
89. Kozak W, Mayfield KP, Kozak A, Kluger MJ. 2000. Proadifen (SKF-525A), an inhibitor of cytochrome P-450, augments LPS-induced fever and exacerbates prostaglandin-E_2 levels in rats. *J. Thermal Biol.* 25:45–50
90. Kozak W, Kluger MJ, Kozak A, Wachulec M, Dokladny K. 2000. Role of cytochrome P-450 in endogenous antipyresis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 279:R455–60
91. Chinetti G, Fruchart JC, Staels B. 2003. Peroxisome proliferator-activated receptors and inflammation: from basic science to clinical applications. *Int. J. Obes.* 27: S41–45
92. Renz H, Henke A, Hofmann P, Wolff LJ, Schmidt A, et al. 1992. Sensitization of rat alveolar macrophages to enhanced TNF-alpha release by in vivo treatment with dexamethasone. *Cell Immunol.* 144:249–57
93. Fantuzzi G, Demitri MT, Ghezzi P. 1994. Differential effect of glucocorticoids on tumour necrosis factor production in mice: up-regulation by early pretreatment with dexamethasone. *Clin. Exp. Immunol.* 96:166–69
94. Fantuzzi G, Galli G, Zinetti M, Fratelli M, Ghezzi P. 1995. The upregulating effect of dexamethasone on tumor necrosis factor production is mediated by a nitric oxide-producing cytochrome P450. *Cell Immunol.* 160:305–8
95. Fantuzzi G, Cantoni L, Sironi M, Ghezzi P. 1993. Inhibitors of cytochrome P450 suppress tumor necrosis factor production. *Cell Immunol.* 150:417–24
96. Carcillo JA, Korzekwa KR, Jones GS, Parise RA, Gillespie DG, et al. 1998. The cytochrome P450 suicide inhibitor, 1-aminobenzotriazole, sensitizes rats to zymosan-induced toxicity. *Res. Commun. Mol. Pathol. Pharmacol.* 102:57–68
97. Crawford JH, Yang SL, Zhou M, Simms HH, Wang P. 2004. Down-regulation of hepatic CYP1A2 plays an important role in inflammatory responses in sepsis. *Crit. Care Med.* 32:502–8
98. Minamiyama Y, Takemura S, Toyokuni S, Imaoka S, Funae Y, et al. 2004. CYP3A induction aggravates endotoxemic liver injury via reactive oxygen species in male rats. *Free Radic. Biol. Med.* 37:703–12
99. Majano PL, Garcia-Monzon C, Lopez-Cabrera M, Lara-Pezzi E, Fernandez-Ruiz E, et al. 1998. Inducible nitric oxide synthase expression in chronic viral hepatitis. Evidence for a virus-induced gene upregulation. *J. Clin. Invest.* 101:1343–52

100. Mitchell S, Ayesh R, Barrett T, Smith R. 1999. Trimethylamine and foetor hepaticus. *Scand. J. Gastroenterol.* 34:524–28
101. Nakajima M, Iwata K, Yamamoto T, Funae Y, Yoshida T, Kuroiwa Y. 1998. Nicotine metabolism in liver microsomes from rats with acute hepatitis or cirrhosis. *Drug Metab. Dispos.* 26:36–41
102. Park CS, Baek HM, Chung WG, Lee KH, Ryu SD, Cha YN. 1999. Suppression of flavin-containing monooxygenase by overproduced nitric oxide in rat liver. *Mol. Pharmacol.* 56:507–14
103. Ryu SD, Kang JH, Yi HG, Nahm CH, Park CS. 2004. Hepatic flavin-containing monooxygenase activity attenuated by cGMP-independent nitric oxide-mediated mRNA destabilization. *Biochem. Biophys. Res. Commun.* 324:409–16
104. Ryu SD, Yi HG, Cha YN, Kang JH, Kang JS, et al. 2004. Flavin-containing monooxygenase activity can be inhibited by nitric oxide-mediated S-nitrosylation. *Life Sci.* 75:2559–72
105. Barbier O, Duran-Sandoval D, Pineda-Torra I, Kosykh V, Fruchart JC, Staels B. 2003. Peroxisome proliferator-activated receptor alpha induces hepatic expression of the human bile acid glucuronidating UDP-glucuronosyltransferase 2B4 enzyme. *J. Biol. Chem.* 278:32852–60
106. Barbier O, Torra IP, Sirvent A, Claudel T, Blanquart C, et al. 2003. FXR induces the UGT2B4 enzyme in hepatocytes: a potential mechanism of negative feedback control of FXR activity. *Gastroenterology* 124:1926–40
107. Barbier O, Villeneuve L, Bocher V, Fontaine C, Torra IP, et al. 2003. The UDP-glucuronosyltransferase 1A9 enzyme is a peroxisome proliferator-activated receptor alpha and gamma target gene. *J. Biol. Chem.* 278:13975–83
108. Barbier O, Girard H, Inoue Y, Duez H, Villeneuve L, et al. 2005. Hepatic expression of the UGT1A9 gene is governed by hepatocyte nuclear factor 4alpha. *Mol. Pharmacol.* 67:241–49
109. Chen YL, Florentin I, Batt AM, Ferrari L, Giroud JP, Chauvelot-Moachon L. 1992. Effects of interleukin-6 on cytochrome P450-dependent mixed-function oxidases in the rat. *Biochem. Pharmacol.* 44:137–48
110. Banhegyi G, Mucha I, Garzo T, Antoni F, Mandl J. 1995. Endotoxin inhibits glucuronidation in the liver. An effect mediated by intercellular communication. *Biochem. Pharmacol.* 49:65–68
111. Monshouwer M, Witkamp RF, Nujmeijer SM, Van Amsterdam JG, Van Miert AS. 1996. Suppression of cytochrome P450- and UDP glucuronosyl transferase-dependent enzyme activities by proinflammatory cytokines and possible role of nitric oxide in primary cultures of pig hepatocytes. *Toxicol. Appl. Pharmacol.* 137:237–44
112. Strasser SI, Mashford ML, Desmond PV. 1998. Regulation of uridine diphosphate glucuronosyltransferase during the acute-phase response. *J. Gastroenterol. Hepatol.* 13:88–94
113. Levesque E, Beaulieu M, Guillemette C, Hum DW, Belanger A. 1998. Effect of interleukins on UGT2B15 and UGT2B17 steroid uridine diphosphate-glucuronosyltransferase expression and activity in the LNCaP cell line. *Endocrinology* 139:2375–81
114. Congiu M, Mashford ML, Slavin JL, Desmond PV. 2002. UDP glucuronosyltransferase mRNA levels in human liver disease. *Drug Metab. Dispos.* 30:129–34
115. Radominska A, Treat S, Little J. 1993. Bile acid metabolism and the pathophysiology of cholestasis. *Semin. Liver Dis.* 13: 219–34
116. Shimada M, Watanabe E, Iida Y, Nagata K, Yamazoe Y. 1999. Alteration of hepatic sulfation by endotoxin. *Jpn. J. Pharmacol.* 80:371–73
117. Song CS, Jung MH, Kim SC, Hassan T, Roy AK, Chatterjee B. 1998. Tissue-specific and androgen-repressible regulation of the rat dehydroepiandrosterone

sulfotransferase gene promoter. *J. Biol. Chem.* 273:21856–66

118. Maheo K, Morel F, Antras-Ferry J, Langouet S, Desmots F, et al. 1998. Endotoxin suppresses the oltipraz-mediated induction of major hepatic glutathione transferases and cytochromes P450 in the rat. *Hepatology* 28:1655–62
119. Choi SH, Kim SG. 1998. Lipopolysaccharide inhibition of rat hepatic microsomal epoxide hydrolase and glutathione S-transferase gene expression irrespective of nuclear factor-kappaB activation. *Biochem. Pharmacol.* 56:1427–36
120. Buetler TM. 1998. Identification of glutathione S-transferase isozymes and gamma-glutamylcysteine synthetase as negative acute-phase proteins in rat liver. *Hepatology* 28:1551–60
121. Maheo K, Antras-Ferry J, Morel F, Langouet S, Guillouzo A. 1997. Modulation of glutathione S-transferase subunits A2, M1, and P1 expression by interleukin-1beta in rat hepatocytes in primary culture. *J. Biol. Chem.* 272:16125–32
122. Voss SH, Park Y, Kwon SO, Whalen R, Boyer TD. 1996. Role of interleukin 6 and corticosteroids in the regulation of expression of glutathione S-transferases in primary cultures of rat hepatocytes. *Biochem. J.* 317(Pt. 2):627–32
123. Voss SH, Whalen R, Boyer TD. 2002. Mechanism of negative regulation of rat glutathione S-transferase A2 by the cytokine interleukin 6. *Biochem. J.* 365:229–37
124. Whalen R, Voss SH, Boyer TD. 2004. Decreased expression levels of rat liver glutathione S-transferase A2 and albumin during the acute phase response are mediated by HNF1 (hepatic nuclear factor 1) and IL6DEX-NP. *Biochem. J.* 377:763–68
125. Chan LM, Lowes S, Hirst BH. 2004. The ABCs of drug transport in intestine and liver: efflux proteins limiting drug absorption and bioavailability. *Eur. J. Pharm. Sci.* 21:25–51
126. Wacher VJ, Silverman JA, Zhang Y, Benet LZ. 1998. Role of P-glycoprotein and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics. *J. Pharm. Sci.* 87:1322–30
127. Schinkel AH, Smit JJ, van Tellingen O, Beijnen JH, Wagenaar E, et al. 1994. Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. *Cell* 77:491–502
128. Schinkel AH, Mayer U, Wagenaar E, Mol CA, van Deemter L, et al. 1997. Normal viability and altered pharmacokinetics in mice lacking mdr1-type (drug-transporting) P-glycoproteins. *Proc. Natl. Acad. Sci. USA* 94:4028–33
129. Trauner M, Meier PJ, Boyer JL. 1998. Molecular pathogenesis of cholestasis. *N. Engl. J. Med.* 339:1217–27
130. Green RM, Whiting JF, Rosenbluth AB, Beier D, Gollan JL. 1994. Interleukin-6 inhibits hepatocyte taurocholate uptake and sodium-potassium-adenosinetriphosphatase activity. *Am. J. Physiol. Gastrointest. Liver Physiol.* 267: G1094–100
131. Green RM, Beier D, Gollan JL. 1996. Regulation of hepatocyte bile salt transporters by endotoxin and inflammatory cytokines in rodents. *Gastroenterology* 111:193–98
132. Whiting JF, Green RM, Rosenbluth AB, Gollan JL. 1995. Tumor necrosis factor-alpha decreases hepatocyte bile salt uptake and mediates endotoxin-induced cholestasis. *Hepatology* 22:1273–78
133. Ogawa K, Suzuki H, Hirohashi T, Ishikawa T, Meier PJ, et al. 2000. Characterization of inducible nature of MRP3 in rat liver. *Am. J. Physiol. Gastrointest. Liver Physiol.* 278:G438–46
134. Denk GU, Soroka CJ, Takeyama Y, Chen WS, Schuetz JD, Boyer JL. 2004. Multidrug resistance-associated protein 4 is up-regulated in liver but down-regulated in kidney in obstructive cholestasis in the rat. *J. Hepatol.* 40:585–91

135. Trauner M, Arrese M, Soroka CJ, Ananthanarayanan M, Koeppel TA, et al. 1997. The rat canalicular conjugate export pump (Mrp2) is down-regulated in intrahepatic and obstructive cholestasis. *Gastroenterology* 113:255–64
136. Vos TA, Hooiveld GJ, Koning H, Childs S, Meijer DK, et al. 1998. Up-regulation of the multidrug resistance genes, Mrp1 and Mdr1b, and down-regulation of the organic anion transporter, Mrp2, and the bile salt transporter, Spgp, in endotoxemic rat liver. *Hepatology* 28:1637–44
137. Kubitz R, Wettstein M, Warskulat U, Haussinger D. 1999. Regulation of the multidrug resistance protein 2 in the rat liver by lipopolysaccharide and dexamethasone. *Gastroenterology* 116:401–10
138. Nakamura J, Nishida T, Hayashi K, Kawada N, Ueshima S, et al. 1999. Kupffer cell-mediated down regulation of rat hepatic CMOAT/MRP2 gene expression. *Biochem. Biophys. Res. Commun.* 255:143–49
139. Hartmann G, Cheung AK, Piquette-Miller M. 2002. Inflammatory cytokines, but not bile acids, regulate expression of murine hepatic anion transporters in endotoxemia. *J. Pharmacol. Exp. Ther.* 303:273–81
140. Zollner G, Fickert P, Silbert D, Fuchsbichler A, Stumptner C, et al. 2002. Induction of short heterodimer partner 1 precedes downregulation of Ntcp in bile ductligated mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* 282:G184–91
141. Geier A, Dietrich CG, Voigt S, Kim SK, Gerloff T, et al. 2003. Effects of proinflammatory cytokines on rat organic anion transporters during toxic liver injury and cholestasis. *Hepatology* 38:345–54
142. Cherrington NJ, Slitt AL, Li N, Klaassen CD. 2004. Lipopolysaccharide-mediated regulation of hepatic transporter mRNA levels in rats. *Drug Metab. Dispos.* 32:734–41
143. Elferink MG, Olinga P, Draaisma AL, Merema MT, Faber KN, et al. 2004. LPS-induced downregulation of MRP2 and BSEP in human liver is due to a post-transcriptional process. *Am. J. Physiol. Gastrointest. Liver Physiol.* 287:G1008–16
144. Ghose R, Zimmerman TL, Thevananther S, Karpen SJ. 2004. Endotoxin leads to rapid subcellular re-localization of hepatic RXRalpha: a novel mechanism for reduced hepatic gene expression in inflammation. *Nucl. Recept.* 2:4
145. Li N, Choudhuri S, Cherrington NJ, Klaassen CD. 2004. Down-regulation of mouse organic anion-transporting polypeptide 4 (Oatp4; Oatp1b2; Slc21a10) mRNA by lipopolysaccharide through the toll-like receptor 4 (TLR4). *Drug Metab. Dispos.* 32:1265–71
146. Piquette-Miller M, Pak A, Kim H, Anari R, Shahzamani A. 1998. Decreased expression and activity of P-glycoprotein in rat liver during acute inflammation. *Pharm. Res.* 15:706–11
147. Sukhai M, Yong A, Kalitsky J, Piquette-Miller M. 2000. Inflammation and interleukin-6 mediate reductions in the hepatic expression and transcription of the mdr1a and mdr1b genes. *Mol. Cell. Biol. Res. Commun.* 4:248–56
148. Hartmann G, Kim H, Piquette-Miller M. 2001. Regulation of the hepatic multidrug resistance gene expression by endotoxin and inflammatory cytokines in mice. *Int. Immunopharmacol.* 1:189–99
149. Hartmann G, Vassileva V, Piquette-Miller M. 2005. Impact of endotoxin-induced changes in P-glycoprotein expression on disposition of doxorubicin in mice. *Drug Metab. Dispos.* 33(6):820–88
150. Miyoshi M, Nadai M, Nitta A, Ueyama J, Shimizu A, et al. 2005. Role of tumor necrosis factor-alpha in down-regulation of hepatic cytochrome P450 and P-glycoprotein by endotoxin. *Eur. J. Pharmacol.* 507:229–37
151. Donner MG, Warskulat U, Saha N, Haussinger D. 2004. Enhanced expression of basolateral multidrug resistance

protein isoforms Mrp3 and Mrp5 in rat liver by LPS. *Biol. Chem.* 385:331–39

152. Lee G, Piquette-Miller M. 2003. 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.* 92:2152–63
153. Li N, Klaassen CD. 2005. Lipopolysaccharide-induced down-regulation of organic anion transporting polypeptide 4 (Oatp4; Slc21a10) is independent of tumor necrosis factor-alpha, interleukin-1beta, interleukin-6, or inducible nitric oxide synthase. *Toxicol. Sci.* 83:197–203
154. Siewert E, Dietrich CG, Lammert F, Heinrich PC, Matern S, et al. 2004. Interleukin-6 regulates hepatic transporters during acute-phase response. *Biochem. Biophys. Res. Commun.* 322:232–38
155. Ros JE, Schuetz JD, Geuken M, Streetz K, Moshage H, et al. 2001. Induction of Mdr1b expression by tumor necrosis factor-alpha in rat liver cells is independent of p53 but requires NF-kappaB signaling. *Hepatology* 33:1425–31
156. Li D, Zimmerman TL, Thevananther S, Lee HY, Kurie JM, Karpen SJ. 2002. Interleukin-1 beta-mediated suppression of RXR:RAR transactivation of the Ntcp promoter is JNK-dependent. *J. Biol. Chem.* 277:31416–22

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