19 Regulation of Drug Metabolizing Enzymes and Transporters in Infection, Inflammation, and Cancer

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19.1 SUMMARY

Under conditions of innate immune system activation (i.e., inflammation), the functions of specific cytochrome P450 enzymes, other drug metabolizing enzymes (DMEs), and drug transporters (DTs) are altered in the liver, small intestine, lung, kidney, and central

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nervous system (CNS). Many of these effects are primarily manifest at the transcriptional/RNA level, leading to corresponding changes in protein levels and function. This not only leads to altered drug and xenobiotic toxicity and action in diseased humans, but also has importance for disease therapy with biologic drugs that target inflammatory mediators or their receptors. Major roles for proinflammatory cytokines such as interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-α (TNFα) are inferred from the abilities of these agents to affect DMEs and DTs in cultured cells and *in vivo*, but the *in vivo* contributions of cytokines to regulation of these proteins in different inflammatory disease states is still poorly understood.

19.2 INTRODUCTION

As is elaborated in detail in the ensuing pages, inflammation and infection in humans or experimental animals are associated with changes in the expression and function of many DMEs and DTs. Especially for the DMEs, in the majority of cases these effects result in an impairment of their function (enzyme or transporter activity), although some proteins can be induced.

It will become evident that the great majority of information in this area comes from studies on the cytochrome P450 (P450) enzymes. However, research on the regulation of other DMEs and DTs is progressing, and will be summarized hereunder. The majority of studies in animals have been performed on acute models of infection or inflammation [e.g., the bacterial lipopolysaccharide (LPS) model]. In most cases where the time course has been studied, the effects are transitory and drug metabolism or disposition normalizes with the resolution of the inflammation. However, there is also the potential for long-lasting effects of disease, as observed for flavin monooxygenase (FMO)-3 that remains downregulated in the livers of mice treated with *Citrobacter rodentium* long after the infection and concomitant colonic inflammation have resolved [1].

19.2.1 Effect of Disease on Clinical Drug Therapy

Downregulation of hepatic DMEs consequent to activation of host defense (the innate immune system) can be expected to reduce the hepatic clearance of drugs that are eliminated by the specific enzymes affected, resulting in elevated plasma levels of drug and possible toxicity if doses are not adjusted. For example, an outbreak of influenza virus was associated with increased incidence of theophylline toxicity in asthmatic children, concomitant with a 67% increase in theophylline half-life (corresponding to approximately a 40% decrease in clearance) [2]. Even relatively modest effects like this clearly pose a risk of drug toxicity and indicate the need for dose adjustment, when the drug affected has a low therapeutic index (such as theophylline, warfarin, and cyclosporine). More recently, a 90% decline in hepatic activity of CYP2D6 in human immunodeficiency virus (HIV)-infected patients was reported [3], indicating the potential for much greater effects on drug clearance in humans.

Conversely, induction of DMEs due to inflammation or infection would be expected to cause elevated clearance and reduced plasma levels of affected drugs, possibly resulting in therapeutic inefficacy. For example, in a review of the literature on pharmacokinetics in HIV/AIDS (acquired immunodeficiency syndrome), Dickinson *et al*. [4] concluded that there was a general trend toward reduced plasma levels

of protease inhibitors (CYP3A4 substrates), especially azatanavir, in people with HIV/AIDS, although no single study showed any significant differences. This would imply the induction of CYP3A4 and/or P-glycoprotein (PGP), although this has not been demonstrated.

The consequences of DT regulation by inflammatory factors may be anticipated. Downregulation of efflux transporters would be expected to result in increased bioavailability and tissue accumulation of drugs, whereas the same effect on uptake transporters would be expected to result in reduced bioavailability and tissue concentrations of drug. The reverse would be true for induction of the transporters.

Overall, the information on the impact of disease on drug metabolism and disposition in humans is scanty, and much more research is needed. However, such studies are very difficult because rarely does the researcher have access to patients with untreated disease, and the ethical issues associated with withholding or delaying treatment are manifest.

19.2.2 Drug–Drug Interactions (DDIs)

Many, if not all, of the effects of inflammatory diseases on drug metabolism are thought to be due to the action of proinflammatory cytokines on hepatocytes and other cells. To date, TNFα, IL-1β, IL-6, and interferons (IFNs) have been implicated as the most important. While TNFα, IL-1, or IL-6 are not clinically used drugs, IFNsα, β, and γ are all used to treat various cancers and are capable of downregulating P450 expression in cell culture and in animals *in vivo*. Therefore, they have the potential to interact with other medications. However, effects reported on drug metabolism in humans are inconsistent [5].

19.2.3 Drug-Disease-Drug Interactions (DDDIs)

The recent advent of the so-called biologic drugs targeting proinflammatory cytokines or their receptors (Table 19.1) has resulted in a new type of drug–drug interaction (DDI) that is disease dependent, which we will call drug-disease-drug interaction (DDDI). Originally, it was thought that biologic drugs did not pose a risk for interactions with small molecule drugs, because the biologics are metabolized by completely different enzymes, and do not inhibit or induce DMEs. However, the results from two animal studies in which the downregulations of hepatic CYP3A enzymes were reversed by a polyclonal antibody to IL-6 [6] or by infliximab, a monoclonal antibody to TNFα marketed for the treatment of arthritis and other autoimmune diseases [7], demonstrated the possibility for disease-dependent biologic-small molecule interactions in humans. Recently, the Food and Drug Administration (FDA) approved a humanized monoclonal antibody to the IL6 receptor, tocilizumab, for the treatment of rheumatoid arthritis. The report of the FDA's Arthritis Committee notes that plasma levels of simvastatin (a CYP3A4 substrate) and omeprazole (a CYP2C19 substrate) were reduced in patients treated with tocilizumab, consistent with the ability of IL-6 to downregulate these P450s in primary human hepatocyte cultures [8]. Thus, biologics can reduce the therapeutic efficacy of small molecule drugs, by relieving the inflammatory downregulation of the enzymes involved in their clearance.

The extent of DDDIs is only beginning to be understood. When a drug neutralizes a cytokine that can directly regulate DMEs in the hepatocyte, a DDDI of the type described might reasonably be expected. However, other cytokines might act

TABLE 19.1 Biologic Drugs Targeted to Inflammatory Diseases

Drug	Target	Diseases/Indications
Adalimumab	TNFα	Rheumatoid arthritis
Certolizumab-pegol	TNFα	Crohn's disease
Etanercept	TNFα	Rheumatoid arthritis
Infliximab	TNFα	Rheumatoid arthritis, Crohn's disease
Golimumab	TNFα	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis
Canakinumab	IL-1β	Cryopyrin-associated periodic syndromes
Rilonacept	IL-1β	Cryopyrin-associated periodic syndromes
Anakinra	IL-1 receptor	Rheumatoid arthritis
Daclizumab	IL-2 receptor	Acute organ rejection, asthma, multiple sclerosis, autoimmune
Basiliximab	IL-2 receptor	Acute organ rejection
Tocilizumab	IL-6 receptor	Rheumatoid arthritis
Ustekinumab	IL-12 and IL-23	Psoriasis
Abatacept	B7, T-cell comodulator	Rheumatoid arthritis

The above drugs are monoclonal antibodies or Fab fragments except anakinra, which is a receptor antagonist; etanercept, which is a cytokine receptor fragment; and abatacept and rilonacept, which are fusion proteins.

redundantly with the one targeted by the biologic, such that no effect would have been seen. On the other hand, it is possible that any drug that resolves inflammation, regardless of its mechanism, has the potential to cause a DDDI by reducing production of the cytokines that act directly on the liver. It remains to be seen whether well-characterized nonbiologic drugs such as nonsteroidal anti-inflammatories might be involved in DDDIs.

19.3 THE INNATE IMMUNE SYSTEM AND ITS ACTIVATION IN INFLAMMATION AND INFECTION

19.3.1 Cellular and Molecular Aspects of the Innate Immune System

Mammals and other host organisms deal with invading organisms via the two branches of the immune system, that is, the innate and the adaptive immune system [9]. The innate immune system has developed to survey the plasma and tissues for signs of foreign organism invasion, and to respond rapidly to eliminate the danger. The adaptive immune system mounts a slower but more specific response, designed to remember the molecular characteristics of a pathogen or toxin and thus enable the host to respond rapidly to a subsequent infection weeks to years later. Cells and molecules associated primarily with innate immunity have been implicated in the modulation of drug metabolism and transport, and therefore we will concentrate on the innate arm of the immune system.

Inflammation is caused by the response of the innate immune system to invading organisms or to tissue damage. It can be thought of as an adaptive homeostatic mechanism that becomes detrimental if inappropriately stimulated or dysregulated [10]. The cellular response of the innate immune system to infection or the presence of damaging toxins is primarily mediated by granulocytic leukocytes of the myeloid

lineage: monocytes, macrophages, neutrophils, mast cells, basophils, and eosinophils [9]. Natural killer (NK) cells, a type of T cell, also participate. The innate immune system is activated by invading pathogens via several families of proteins, called *pattern-recognition receptors*, which recognize structural motifs common to many invading pathogens or the molecules they secrete [11]. These pathogen-associated molecular patterns (PAMPs), described in detail in the ensuing section, are characteristics of molecules such as LPS, double-stranded viral RNA, and bacterial muramyl dipeptide.

The pattern-recognition receptors are expressed primarily in macrophages, but also in monocytes and neutrophils as well as in fixed tissue cells such as epithelial cells and keratinocytes [9]. Engagement of PAMPs with their receptors initiates specific signaling pathways in the cells, which result in the secretion of cytokines such as TNFα, IL-1, IL-6, and IFNγ to initiate the inflammatory response. TNFα and IL-1 are so-called proinflammatory cytokines, whereas IL-6 can be either pro- or anti-inflammatory. These initiator cytokines then activate other immune and nonimmune cells to produce additional cytokines and prostanoids, as well as chemokines (chemotactic cytokines) such as macrophage inflammatory protein- 1α, (MIP- 1α, chemotactic for neutrophils and NK cells) monocyte chemotactic protein- 1α (MCP-1, chemotactic for monocytes and basophils), and IL-8 (chemotactic for neutrophils). Chemokines induce the expression of adhesion molecules on host cells so that effector cells such as neutrophils and NK cells, recruited to the site of injury by the chemokines, attach to the host cells. The identities of the chemokines induced, and thus the immune cells recruited, depends on the initial cytokine pattern which in turn depends on the initiating signal and the tissue(s) in which they occur [12].

Of special interest for drug disposition are the specialized macrophages of the liver, Kupffer cells (KCs), which represent an estimated 80–90% of the fixed macrophages in the body [13]. KCs are found in the sinusoidal lumen, where they are well positioned to detect bacteria, their toxins, and breakdown products absorbed from the gastrointestinal tract. When activated by bacterial endotoxin or by complement, KCs release TNFα, IL-1, and IL-6 as well as nitric oxide, superoxide (from NADPH oxidase), prostaglandins, and thromboxanes. Therefore, it should be apparent that the local concentrations of these agents in the vicinity of the hepatocytes is likely to be much greater during inflammation caused by, for example, the injection of LPS than during inflammation elicited at a distant anatomical site. In the latter case, regulation of the hepatocytes will occur via circulating cytokines.

19.3.2 Pattern-Recognition Receptors

The best-understood family of pattern-recognition receptors is the family of integral membrane glycoproteins called *toll-like receptors* (TLRs) [11]. TLRs 1–9 are common to humans and mice, whereas the additional species-specific TLRs (TLR10 in humans and TLRs 11–13 in mice) are of unknown function. The TLRs recognize PAMPs associated with bacterial, fungal, and viral organisms (Table 19.2) [11]. TLR4, the best-characterized and prototypic TLR, was discovered as the gene whose mutation rendered mice (HeJ strain) insensitive to LPS. However, binding of LPS to TLR4 absolutely requires the presence of a soluble accessory protein MD-2 [14]. CD14 is another TLR4 accessory protein that sensitizes cells to LPS by facilitating ligand transfer to the receptor complexes and/or directing these complexes to signaling centers such as lipid rafts [14]. There is recent evidence that CD14 may also fulfill similar functions with

TABLE 19.2 Characteristics of the Toll-Like Receptors

TLR	Ligands	Signaling Pathways	Cellular Context	Hepatic Expression
1	Triacyl lipoprotein	MyD88/TIRAP	PM	SE KC SC
2	Lipoproteins	MyD88/TIRAP	PM	H SE KC SC
3	ds RNA	TRIF/TRAM	Endosomes	H SE KC SC
4	LPS	MyD88/TIRAP TRIF/TRAM	PM	H SE KC SC
5	Flagellin	MyD88/TIRAP	PM	SE KC SC
6	Diacyl lipoprotein Zymosan	MyD88/TIRAP	PM	SE KC SC
7	ss RNA, siRNA	MyD88/TIRAP	Endosomes	H
8	ss RNA	MyD88/TIRAP	Endosomes	SE KC SC
9	Unmethylated CpG-DNA	MyD88/TIRAP	Endosomes	SE KC SC

Abbreviations: PM, plasma membrane; H, hepatocytes; SE, sinusoidal endothelial cells; KC, Kupffer cells; SC, stellate cells.

TLR2 and other TLRs. For TLR4, CD14 also directs whether the responses will be via the MyD88/Mal or TRIF-TRAM (TIR-domain-containing adapter-inducing interferon-β/TRIF-related adaptor molecule) pathways (see below), this being dependent on the ligand [14].

While most TLRs homodimerize in response to ligand binding to initiate signaling, TLR2 heterodimerizes with either TLR1 or TLR6 to recognize bacterial, mycobacterial, and fungal products. Thus, TLR1/2 recognizes triacyl lipopeptides produced by gram-positive bacteria and mycobacteria, and TLR1/6 recognizes diacyl lipopeptides and fungal zymosan. TLR5 recognizes flagellin from flagellated bacteria.

TLRs 1, 2, 4, 5, and 6 are expressed on cell membranes, but TLRs 3, 7, 8, and 9 are found in intracellular membranes where they recognize PAMPs associated with intracellular pathogens. TLR3 recognizes double-stranded viral RNA, and is the receptor for the commonly used synthetic agonist polyrI.rC. TLRs 7 and 8 recognize single-stranded viral RNA, and TLR9 distinguishes unmethylated CpG motifs associated with DNA from viral and bacterial pathogens.

The TLRs (mainly 2 and 4) also recognize damage-associated molecular patterns (DAMPs) on host molecules such as heat shock proteins and hemin, so that inflammation consequent to different types of tissue or cellular damage is also dependent on TLR2 or TLR4. There is some debate as to whether DAMPs themselves activate TLRs, or if they act by sensitizing cells to low levels of PAMPs [15].

Upon ligand binding, the TLRs dimerize to initiate signal transduction through two pairs of adaptor molecules: MyD88 and Mal/TIRAP (toll-interleukin 1 receptor (TIR) domain containing adaptor protein); or TRIF and TRAM (Fig. 19.1). However, only TLRs 2 and 4 need Mal/TIRAP or TRAM (Fig. 19.1). Both pathways result in the activation of NF-κB, a transcription factor that is a master regulator of inflammatory gene expression, as well as activation of MAP (Mitogen Activated Protein) kinases that can regulate other transcription factors such as AP-1. Among the many targets of NF-κB are proinflammatory cytokine genes such as IL-1, TNF, and IL-6, and also several hepatic acute-phase genes. Signal transduction via TRIF/TRAM results in the activation of transcription factors IRF3 and IRF7, causing the induction of IFNs α and β, which have antiviral activities. Activation of NF-κB and MAP kinase (MAPK)

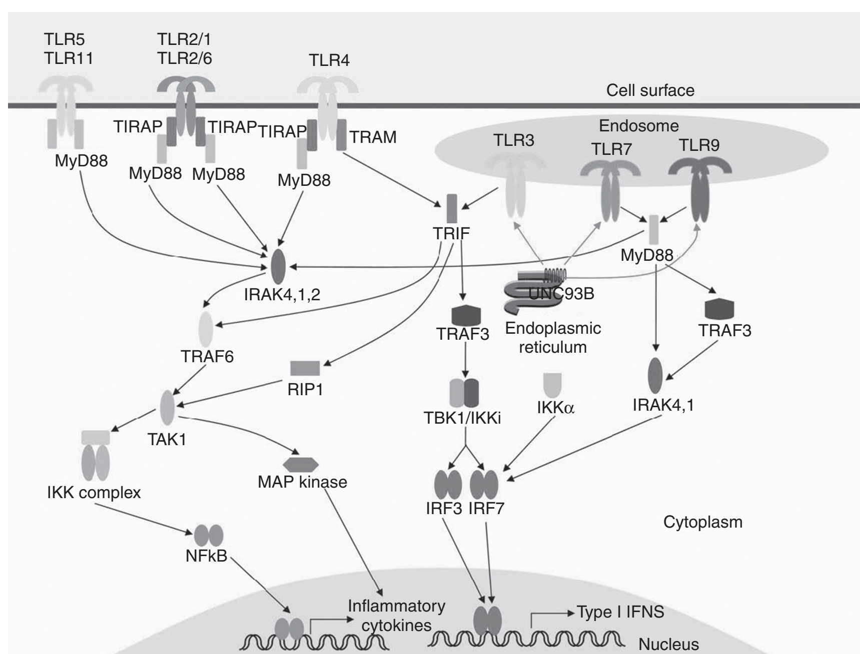

Figure 19.1 TLRs and their cellular signaling mechanisms. *Source:* Reprinted from Kumar H, Kawai T, Akira S. Biochem Biophys Res Commun 2008;388 with permission from Elsevier. (See color insert.)

activation through the two adaptor molecules may be kinetically different and also cell-type dependent. Thus, the result of activation of a given TLR in two different cell types can be different [16].

While TLRs 1, 5, 6, 8, and 9 have not been reported on hepatocytes, they are all expressed in liver nonparenchymal cells (Table 19.2). Moreover, agonists of all TLRs evoked TNFα and IL-6 release by KCs, except for TLR5 that only evoked IL-6 release [16]. TLR3 and TLR4 agonists stimulated IFNβ release from KC as well. Liver sinusoidal epithelial cells released TNFα in response to TLR2, 3, 4, and 8 activation; and IL-6 in response to TLR3 or 4 activation [16]. Similarly, stellate cells express mRNAs for all nine TLRs, especially when activated [17]. Thus, any TLR agonist has the potential to affect hepatocyte DME and DT expression either directly or indirectly.

The roles of TLRs in regulation of DMEs and DTs have been explored to a limited extent. Perhaps not surprisingly, the downregulation of P450 enzymes [18–20] as well as of UDP-glucoronosyltransferase 1a1 (UGT1A1) [19] and the uptake transporter Oatp4 [21] in the LPS model of inflammation requires a functioning TLR4. On the other hand, the regulation of hepatic P450 enzymes in the liver during intestinal infection with *C. rodentium* is independent of TLR4 [20]. This demonstrates that gram-negative bacterial infection can influence hepatic gene expression via different mechanisms.

A second family of pattern-recognition receptors is the NLR (nucleotide-binding, leucine-rich repeat-containing) family, of which there are more than 20 in humans [22]. These intracellular sensors detect PAMPs such as muramyl dipeptide, LPS, flagellin, and bacterial or viral RNA, as well as DAMPs such as uric acid crystals, exhibiting significant overlap with TLR ligands. Ligand binding of NLRs results in

nucleotide-dependent activation of a large protein complex called the *inflammasome*, that in turn results in cleavage of procaspase-1 [22]. Active caspase-1 then cleaves pro-IL-1 and pro-IL-18 to their active forms, initiating an inflammatory response. NLR ligand binding can also mediate the activation of NF-κB and MAP kinase pathways, which further stimulate the production of inflammatory cytokines, antimicrobial peptides, and reactive oxygen species [23]. In addition, NLR activation can be associated with both caspase-1-dependent and -independent cell death (specialized mechanisms of necrosis). This denies intracellular pathogens a cell in which to replicate, and also results in release of cellular components that can stimulate inflammation via TLRs [22].

The potential roles of NLRs and the inflammasome in regulation of DMEs during infection and inflammation are unknown. Mouse hepatocytes express the NLRs NOD1 and NOD2 and respond to NOD1 ligands with the activation of NF-κB and MAP kinases [24]. Hepatic sinusoidal endothelial cells are capable of mounting an Nalp3 inflammasome response in response to DNA from apoptotic hepatocytes [25]. The potential for NLR involvement in DME regulation will be an important area of future research.

19.3.3 The Acute-Phase Response and the Liver

The acute reaction of the body to infection or tissue injury is termed the *acute-phase response* (*APR*), which encompasses all of the cellular and molecular events described above as well as the inflammatory symptoms of fever, redness, swelling, and pain that accompany them. The hepatic component of the APR includes the increased synthesis and secretion of a battery of proteins called *acute-phase proteins* (*APPs*) or *acute-phase reactants* [26,27] within a few hours of the initiating stimulus, and the reduced synthesis of other hepatic proteins called *negative APPs* (such as albumin). Thus, the many DMEs and DTs that are downregulated in inflammation can be considered to be negative APPs. APP synthesis is regulated largely by IL-1, TNFα, and IL-6, with IL-6 playing the dominant role [26]. In addition to acting directly on hepatocytes, however, IL-1 and TNFα can also stimulate KCs to release IL-6, affecting APP synthesis indirectly [27].

During chronic inflammation, serum levels of APPs are often elevated and are used as markers of inflammatory burden in humans. Because their expression and secretion integrate multiple upstream inflammatory signals including proinflammatory cytokines, APP levels tend not to fluctuate as much as those of the cytokines which are relatively short-lived [28]. Thus, serum APPs are being used to assess human health and predict the outcomes of some diseases including cancer [28].

19.4 CONSIDERATIONS FOR PREDICTING THE EFFECTS OF INFLAMMATION ON DRUG DISPOSITION AND DRUG-DISEASE-DRUG INTERACTIONS

The ultimate goal of research in this area is to develop biomarkers and decision-making tools that will allow prediction of changes in drug metabolism and disposition in an individual or a population due to a specific disease, and the prediction or exclusion of DDDIs in people treated with anti-inflammatory biologic drugs. This would allow physicians to prescribe safer and more efficacious drug regimens for their patients, and also facilitate the drug development process. To achieve this goal, we must fully understand the multiple factors that can alter drug metabolism during inflammation and infection, and also the mechanisms by which these effects are achieved.

19.4.1 Roles of Cytokines and Other Mediators

Proinflammatory cytokines such as TNFα and IL-6 are capable of potent regulation of DMEs and DTs in hepatocytes and some other cell types, with a degree of specificity. Studies in cytokine or cytokine receptor knockout mice, or studies using cytokine antibodies, provide evidence for *in vivo* roles of these cytokines in certain inflammatory disease states. However, the effect of removing a cytokine either genetically or immunologically is dependent on the disease model and is not generalizable to all DMEs or transporters. This is most likely because of redundancy and/or cross-talk of cytokine pathways, as well as qualitative, quantitative, spacial, and temporal differences in cytokine secretion in different disease states.

As mentioned above, studies on cytokine regulation of DMEs and DTs to date have focused mainly on the ones known to be involved in hepatic APP regulation. However, there are receptors for many other cytokines and chemokines on hepatocytes and nonparenchymal cells in the liver (Table 19.3), and there is a need to discover which of these could be involved in DME and transporter regulation.

In certain diseases, DME and transporters could be regulated by factors other than cytokines. Activation of TLRs or other pattern-recognition receptors on hepatocytes could trigger changes in DME expression. Nonproteinaceous inflammatory mediators such as prostaglandins, or proteins or small molecules secreted by invading bacteria or parasites could also play a role. However, good evidence for or against such regulation is lacking at the present time.

19.4.2 Inflammation and Chronic Diseases

Research on the impact of inflammation on DMEs and DTs has tended to focus on acute inflammation and diseases or models of diseases that have inflammation as a

TABLE 19.3 Hepatic Target Cells of Cytokines and Chemokines

Cytokine/chemokine	Target Cells in Liver	References
IL-1	H SE KSC	29–32
IL-2	H K SC	33–35
IL-6	H SE KSC	36–38
IL-8	H	39
IL-12	Not described	—
IL-13	H SC	40,41
IL-17	H L	42,43
IL-21	Not described	—
TNFα	K	44
IFNα/β	H K SC	45,46
IFNγ	H SE K SC	31,47,48
MCP-1	H K SC	49–51
MIP-1α	K	52
RANTES	K SC	52

In this table, a cell type is designated to be a target cell if receptors or a specific functional response have been detected. *Abbreviations*: L, liver-cell type unspecified; H, hepatocytes; SE, sinusoidal endothelial cells; KC, Kupffer cells; SC, stellate cells.

TABLE 19.4 Disease States with Inflammation as a Primary or Underlying Component

Primary	Underlying
Infection, septic shock	Cancer
Alcoholic and nonalcoholic fatty liver disease	Congestive heart failure
Rheumatoid arthritis	Hypertension
Gouty and osteoarthritis	Atherosclerosis
Tendinitis	Sickle cell disease
Fibromyalgia	Multiple sclerosis
Lupus (SLE)	Parkinson's disease
Asthma, chronic obstructive pulmonary disease (COPD)	Alzheimer's disease
Inflammatory bowel diseases	Chronic kidney disease/hemodialysis
Psoriasis	Obesity, metabolic syndrome, diabetes
Injury	

cause or primary component (Table 19.4). However, inflammation is now recognized as a condition associated with, or underlying, many chronic diseases and therefore has the potential to impact drug metabolism and disposition (Table 19.4). For example, inflammation is intimately involved in the development and progression of cancer, with inflammatory cytokines being produced both by immune cells and by the cancer cells themselves [53]. Cancer in humans is associated with reduced activity of CYP3A4, as detected by reduced clearance of its substrates erythromycin and docetaxel [53]. Clearance was negatively correlated with serum concentrations of APP and IL-6 levels [53,54], suggesting that the effect is dependent on the degree of inflammation associated with the disease. Examples of other diseases that have inflammation as an underlying component will be presented, but much more work is needed in this area.

19.4.3 Biomarkers

It will be apparent from the above discussion that cytokines themselves could be prognostic biomarkers for drug metabolism and disposition. This will be especially true for diseases in which a given cytokine is demonstrated to be mechanistically involved. Likewise, serum APP levels are used to measure inflammatory loads and are associated with disease outcomes such as in cancer [53]. C-reactive protein (CRP) is an APP that is readily detectable at low concentrations in human plasma, and which is measured in many routine health screening tests. As mentioned above, its plasma levels are negatively correlated with CYP3A4-catalyzed drug clearance in cancer patients, and it deserves further scrutiny as a predictive biomarker in cancer and other inflammatory diseases. If CRP levels are elevated, then one can infer that IL-6 and/or TNFα signaling pathways have been activated in hepatocytes suggesting that some DMEs and/or DTs will be affected. However, if other mechanisms of DME regulation predominate in a particular disease state, changes in drug metabolism or disposition may well occur before or without changes in APP secretion. This illustrates the need to understand the mediators and mechanisms of DME and DT regulation.

19.5 REGULATION OF THE CYP1 FAMILY

Sections 19.5–19.8 focus on hepatic expression of the major drug metabolizing P450 enzymes.

19.5.1 Bacterial Infection

Bacterial infections have been reported to downregulate protein and (or) CYP1A-associated activity in humans infected with *Helicobacter pylori* [55] or bacterial pneumonia [56]; pigs infected with *Actinobacillus pleuropneumoniae* [57]; and both mice and *Cyprinus carpio* (carp) infected with *Listeria monocytogenes* [58–60]. Following intracerebroventricular (i.c.v.) injection of *L. monocytogenes* in rats, CYP1A activity was significantly elevated at 48 h but returned to normal levels by 72 h [61]. In mice that developed hepatitis due to *Helicobacter hepaticus* infection, Cyp1a protein levels were induced [62], but the infection of mice with *C. rodentium*, a mouse intestinal pathogen, had no effect on Cyp1a2 mRNA levels measured seven days post infection [63,64].

19.5.2 Viral Infection

It has been known for several decades that humans infected with the influenza virus have depressed CYP1A activity as shown by their depressed theophylline clearance [2,65]. Hepatitis caused by infection with either the B or C virus also depressed CYP1A-associated activities and/or proteins in humans and mice [66–68]. Infection with HIV, on the other hand, had no significant effect on CYP1A2 activity as determined by urinary caffeine metabolite ratios [3].

19.5.3 Parasitic Infection

Both the hookworm (*Ancylostoma ceylanicum*) and liver fluke (*Fasciola hepatica*) downregulate hepatic mammalian CYP1A activity [69–71]. The caffeine and theophylline clearance of both children and adults infected with *Plasmodium falciparum* malaria is reduced [72,73]. The infection of rodents with *Plasmodium berghei* (ANKA strain), *P. falciparum*, or *Plasmodium chabaudi chabaudi* depresses their CYP1A activity levels [74–77]. Mice with schistosomiasis (infection of *Schistosoma mansoni*) have reduced hepatic 7-methoxy- and 7-ethoxyresorufin-*O*-deethylase (EROD), both Cyp1A-associated activities, during the early phases of infection and upregulation in chronic infection [78–80]. The hepatic microsomes of rats infected with *Taenia taeniformis* had lower EROD activity than those of rats that were uninfected [81].

19.5.4 Sterile Inflammation

Injection of LPS is a model of bacterial sepsis, and evokes an acute systemic inflammatory response. Owing to its ease of use and the large responses observed, it has been used in many laboratories to study how inflammation can regulate DME and DT expression. It is important to keep in mind that this model of end-stage disease is unlikely to predict how these systems will be affected in diseases where inflammation

is more localized and/or less fulminant. Most reports indicate that i.p. injection of LPS, derived from either *Escherichia coli* or *Salmonella abortus equi*, results in the downregulation of CYP1A mRNA, protein levels, or activity in of rats or mice [64,82–84] as well as human beings [85,86]. However, LPS upregulates EROD activity in juvenile carp [87].

The administration of dextran sulfate sodium (DSS) is a well-characterized model of chemically induced inflammatory bowel disease (IBD) that has been used to study the regulation of hepatic P450 function in animals. In (DSS)-induced colitis as well as in collagen-induced arthritis or local inflammation induced by subcutaneous injection of casein or silver nitrate, downregulations of CYP1A-associated activities were observed [82,88,89]. The induction of cirrhosis by either carbon tetrachloride, thioacetamide or by bile duct ligation has been reported to cause the downregulation of CYP1A [90,91], which is likely to have inflammatory components. Conversely, Nakajima *et al*. [91] reported that D-galactosamine-induced hepatitis does not affect rat CYP1A protein levels. While both the Bacillus Calmette Guérin (tuberculosis, BCG) and influenza vaccines have been reported to downregulate theophylline clearance in humans [92,93], in another study the BCG vaccine given to rats did not affect phenacetin O-de-ethylation [94].

19.5.5 Cancer

Rodents with different sarcomas have been reported to have decreased CYP1A protein and (or) activity when compared to animals free of this condition [54,95]. In humans, the presence of hepatocellular carcinoma was reported to both to have no effect [68] and to downregulate phenacetin-deethylation [67], an activity which is associated with CYP1A.

19.6 REGULATION OF THE CYP2 FAMILY

19.6.1 CYP2A

Unlike most other CYPs, the CYP2A enzymes are often upregulated in inflammation or infection. This could be due to the fact that these enzymes are regulated by the redox-sensitive transcription factor Nrf2 [96,97].

Murine hepatitis caused by bacterial infection with *H. hepaticus* has been reported to elevate levels of Cyp2a5 [62], while infection with *C. rodentium* did not affect mRNA levels of the same enzyme [63,64]. In mice, hepatitis B virus infection has been shown to upregulate Cyp2a5 protein levels as well as activity [66,98,99]. In human beings on the other hand, when compared to uninfected controls, those infected by the hepatitis A virus had decreased coumarin-7-hydroxylation (a marker of CYP2A6 activity) [100], while infection with the hepatitis B and C viruses increased CYP2A6 protein levels [101].

The effect of parasite infestation on CYP2A-dependent coumarin 7-hydroxylation has been investigated in both rats and mice. Female C57BL/6 mice were not affected by infection with either *P. berghei* or *P. chabaudi chabaudi,* but age-matched animals with a DBA/2 background had elevated Cyp2a5 activity [76]. In rodents infected with *T. taeniformis* [81,102] and hamsters infected with the liver fluke, *Opisthorchis*

viverrini [103] the activity and (or) protein levels of CYP2As were elevated. Using mice suffering from schistosomiasis, Conte *et al*. [78] reported that there was no change in coumarin 7-hydroxylase activity but Manhaes-Rocha *et al*. [79] noted that while infestation did not change this activity in females, there was significant downregulation in male mice.

The administration of *E. coli* LPS downregulates Cyp2a5 mRNA levels but not the 7α-hydroxylation of testosterone in several strains of mice [20,64,83,84,104,105]. Using a cDNA expression array, Fang *et al*. [106] reported the downregulation of CYP2A1 in rats given 0.5 mg/kg *S. abortus equi* LPS. Administration of lipotechoic acid, a component of gram-positive bacteria and a TLR2 agonist, transiently downregulated hepatic Cyp2a4 [107]. Colitis induced by 3% DSS in drinking water over seven days did not affect Cyp2a5 mRNA levels in the mouse [20].

19.6.2 CYP2B

Bacterial infections tend to downregulate CYP2B isoforms. The infection of either mice or rats with *L. monocytogenes* resulted in lower rates of CYP2B-dependent 7-pentoxyresorufin-O-dealkylation (PROD) and 7-benzyloxyresorufin-O-dealkylation (BROD), respectively [59,61]. Pigs infected with *A. pleuropneumoniae*, mice infected with *C. rodentium,* and tuberculous guinea pigs all exhibited downregulated levels of CYP2B isoforms [20,57,64,108].

Humans infected with hepatitis B or C have been reported to have higher levels of hepatic CYP2B6 than uninfected controls, as assessed via immunohistochemical detection [101]. On the other hand, transgenic hepatitis V virus (HBV) mice had CYP2B protein levels and pentoxyresorufin *O*-dealkylase (PROD) activity comparable to ordinary mice [66,98]. Parasitic infection with liver flukes (*F. hepatica*) downregulated the N-demethylation of benzphetamine in hepatic microsomes of rats [70] and sheep [109]. In mice, infection with malaria downregulates BROD activity in a strain- and time-dependent pattern [75,110]. When using DBA/2 and Swiss Webster mice, Manhaes-Rocha *et al*. [79] reported that schistosomiasis generally did not affect Cyp2b-associated activity, while Conte *et al*. [78] reported a consistent downregulation of the same. In a different model of parasitic infection, microsomes from rats infected with tapeworms (*T. taeniformis)* had a lower activity of PROD than their uninfected counterparts [81].

The administration of *E. coli* LPS downregulates CYP2B in human beings [85,86], rodents [20,64,111], and in cell culture [112]. The TLR2 agonist lipotechoic acid greatly downregulates Cyp2b10 in mouse liver via a KC-dependent mechanism [107]. The downregulation of CYP2B isoforms has been reported for several chemically induced inflammatory conditions including collagen-induced arthritis [88] and thioacetamide-induced cirrhosis in the rat and DSS-induced colitis in the mouse [20] but not D-galactosamine-induced hepatitis of the rat [91]. Male Fisher 344 rats with a pituitary mammotropic tumor had decreased CYP2B activity, measured by hexobarbital sleeping time, as compared to cancer-free animals [113].

19.6.3 CYP2C

Bacterial infection of mice with *C. rodentium* or *L. monocytogenes* as well as the guinea pig with tuberculosis downregulated various CYP2C mRNAs or activities

[60,63,108]. Viral infections also tend to downregulate CYP2C-related activity. Mice infected with encephalomyocarditis virus and humans carrying the HIV or diagnosed with viral hepatitis all had downregulated CYP2C activity [98,114–117]. Callahan *et al*. [118] reported that after a single intravenous dose of the recombinant adenovirus serotype 5 vector, ranging from 5.7×10^6 to 5.7×10^{12} virus particles per kilogram, the activity and mRNA levels of CYP2C11 were upregulated. In a subsequent publication the authors reported that the adenovirus, administered without a transgene, suppressed CYPC11 activity [119]. The authors concluded that the immunogenic and biological nature of a transgene cassette can influence changes in the 2C11 isoform and can be used to study part of the host response to viral infection, via its action on TLR3. Seminal work by Renton and Mannering [120] found that the double-stranded RNA poly I:C, an "interferon inducer" and TLR3 agonist, reduced hepatic content and activities of unspecified P450 enzymes. Its administration to rats was subsequently shown to downregulate CYP2C11 and 2C12 mRNAs and proteins [121,122].

The demethylation of aminopyrine, used as a marker of CYP2C activity is mainly metabolized by CYP2C11 in male rats [123]. Parasitic infections have been reported to downregulate aminopyrine-N-demethylation activity in several mammals including hamsters infected with *Leishmania donovani* [124] or *A. ceylanicum* (hook worm) [69], rats and sheep infected with *F. hepatica* (liver fluke) [125,126], and mice suffering from schistosomiasis [80].

Regardless of the route of administration, whether i.p or by i.c.v. injection, the administration of LPS from *E. coli* or *S. abortus equi* downregulates the levels of CYP2C mRNAs, protein expression and activity [20,64,82,83,106,127]. Mice administered an i.p injection (40 mg/kg) of bacillus Calmette-Guerin vaccine had normal levels of Cyp2c29 after 24 h [128], but the influenza vaccine has been reported to decrease aminopyrine clearance in humans [129]. In rodents, barium sulfate, carrageenan, celite, D-galactosamine, and kaolin have been used as models of sterile inflammation and have resulted in the reduction of CYP2C11 activity and (or) protein in rats [82,91, 130–132] and Cyp2c29 mRNA in mice [20].

Several reports have been made of the downregulation of CYP2C isoforms by cancer including unspecified metastatic cancers in humans [133], Murphy-Sturm lymphosarcoma, pituitary mammotropic tumor, and Walker 256 carcinosarcoma in rats [95,113]. Interestingly, the Engelbreth-Holm-Swarm sarcoma in mice upregulated Cyp2c39 and did not affect Cyp2c37 mRNA [134].

19.6.4 CYP2D

Bacterial infection with *C. rodentium* infection in female mice has been reported to downregulate Cyp2d22 and upregulate Cyp2d9 mRNA levels up to 10 days post infection [63,64]. Using male Wistar rats, Glazier *et al*. [77] reported that there was no significant difference in CYP2D1 activity between control animals and those infected with *P. berghei*, as measured by the α-hydroxylation of metoprolol.

Perhaps in one of the most dramatic demonstrations of the effects of infection on human DMEs, Jones *et al*. [3] reported that compared with healthy volunteers,

HIV-infected subjects had 90% lower CYP2D6 activity determined by the O-demethylation ratio of dextromethorphan metabolites.

LPS downregulated Cyp2d22 mRNA levels in C57BL/6 mice, while levels of Cyp2d9 were induced at 24 h in Refs 20 and 64. Compared to healthy individuals, humans with systemic lupus erythematosus had a decreased ability to convert debrisoquine to 4-hydroxydebrisoquine [135]. While treatment of rats with 2,4,6-trinitrobenzene sulfonic acid resulted in the downregulation of lidocaine metabolism [136], propranolol-7-hydroxylation was neither affected by DSS nor LPS treatments [82]. Treatment of mice with DSS did not affect Cyp2d9 but upregulated Cyp2d22 [20]. The expression of CYP2D was downregulated in rats with carrageenan-induced granuloma [137].

When proteomic profiling of mouse hepatic tissue was performed by multiplexed tandem mass spectrometry after isobaric tag for relative and absolute quantitation (iTRAQ) labeling it was reported that Engelbreth-Holm-Swarm sarcoma downregulated Cyp2d9 but did not affect the expression of either Cyp2d10 or 2 d26 [134].

19.6.5 CYP2E

Bacterial infections in the pig (*A. pleuropneumoniae*) and mouse (*C. rodentium*) have been reported to depress CYP2E1 levels [57,63,64]. In mice, the hepatitis B virus upregulated Cyp2e1-associated 4-nitrophenol hydroxylation [66], and a retroviral infection resulted in increased Cyp2e1 activity at week 8 that returned to normal levels by week 16 [138]. In a malarial parasitic infection model, mice infected with *P. berghei* had increased Cyp2e1-associated activity [75], while in rats CYP2E1 activities were either upregulated or not affected [74,139]. Swiss Webster rats with schistosomiasis had decreased 4-nitrophenol hydroxylase activity at 90 days post infection [78], but only infected male rats showed significant elevation of *N*-nitrosodimethylamine N-demethylation at 30 days post infection [79]. While infection of female rats with *T. taeniformis* did not have a significant effect on 4-nitrophenol hydroxylase activity [81], hamsters infected with leishmaniasis or hook worms (*A. ceylanicum*) as well as sheep and rats infested with liver flukes (*F. hepatica*) all had depressed CYP2E1-associated activity compared to control animals [69,109,124,125].

The administration of LPS to rats and mice has been demonstrated to downregulate both expression and activity of CYP2E1 [20,64,82–84,104,106,111,127], although in one study CYP2E1 mRNA was induced [140]. Neither inflammation induced by kaolin nor D-galactosamine had significant effects on CYP2E1 protein levels of rats [91,132]. DSS-induced colitis suppressed 4-nitrophenol hydroxylase activity in rats but had no significant effect on mRNA levels in mice [20,82]. Administration of the tuberculosis vaccine to rats downregulated chlorzoxazone 6-hydroxylation [94], while in humans CYP2E1 activity is not altered by influenza vaccination [141]. In contrast, Muntane *et al*. [137] reported that rats with carrageenan-induced granuloma showed a strong depression of CYP2E1 RNA during the acute phase and recovered during the chronic phase. The presence of Engelbreth-Holm-Swarm sarcoma in mice and of metastatic cancers in human beings have both been reported to have no effect on CYP2E1 expression [133,134].

19.7 REGULATION OF THE CYP3 FAMILY

19.7.1 Infections

Bacterial infections have been reported to downregulate mouse Cyp3a11, 3a25, and 3a41 as well as rat CYP3A2 [61,63,64]. Critically ill patients with septic shock have been reported to be unable to metabolize midazolam [142]. Both humans and rodents infected with different forms of malaria exhibit downregulation of CYP3A activity [74,139,143]. While infection with hepatitis B or C virus upregulates CYP3A proteins [66,101], HIV-infected subjects had 18% lower hepatic CYP3A4 activity compared with age and sex-matched healthy volunteers [3]. Following a single intravenous dose of the recombinant adenovirus serotype 5 vector, the activity and mRNA levels of rat CYP3A2 were downregulated [118].

19.7.2 Sterile Inflammation

Treatment with LPS causes downregulation of CYP3A1 and 3A2 in rats, and Cyp3a11, 3a25, and 3a41 but not Cyp3a13 in mice [20,64,82–84,104,127,128,144,145]. The TLR2 agonist lipotechoic acid causes a moderate and transient downregulation of Cyp3a11 in mouse liver [107]. Administration of the TLR3 ligand poly rI:C to rats downregulates CYP3A2 [146]. Humans with rheumatoid arthritis had the same amount of urinary 6β-hydroxycortisol as individuals who did not [147], but those with systemic lupus erythematosus, another inflammatory condition, had higher estrogen 16α-hydroxylase activity [148]. Downregulation of rat hepatic CYP3A mRNAs, proteins, and activities has been observed in two different models of arthritis [6,7].

Both rats and mice treated with the tuberculosis vaccine had reduced CYP3A-associated activity [94,128], while humans immunized against the influenza virus had similar CYP3A activity measured by erythromycin breath test as those not immunized [149]. Treatment of rats with the irritants barium sulfate, celite, D-galactosamine, or kaolin did not affect CYP3A2 protein levels [91,132], while induction of a local inflammatory response with turpentine in the rabbit resulted in the downregulation of CYP3A6 protein [150]. In rats, carrageenan-induced granuloma downregulated CYP3A1 mRNA and catalytic activity [137].

19.7.3 Cancer

There is good evidence that CYP3A-mediated clearance is inhibited in people with advanced cancer. Erythromycin clearance was reduced, and negatively correlated with plasma IL-6 and acute-phase protein markers, in individuals with various different associated cancers [53]. Another study found similar results with cancer patients having decreased midazolam clearance and increased exposure to docetaxel [151]. An earlier study on metastatic cancers found no effect on CYP3A protein levels in surgical liver samples [133]. In mice transgenic for a CYP3A4 promoter-β-galactosidase reporter gene, implantation of a murine sarcoma caused downregulation of the transgene as well as the native Cyp3a11 mRNA [54]. These were associated with elevated serum levels of IL-6.

19.8 REGULATION OF THE CYP4 FAMILY

19.8.1 CYP4A

Compared to uninfected animals, mice infected with *C. rodentium* had significantly lower hepatic levels of Cyp4a10 and 4a14 mRNA, and CYP4As were the most profoundly affected of all P450s [63,64]. Infection of mice with the parasite *S. mansoni* resulted in depressed Cyp4a protein levels in the liver [80].

In rats, we found that *E. coli* LPS treatment upregulated CYP4A2 and 4A3 mRNA levels [127]. While there was no difference between the ability of control and treated male Sprague-Dawley rats to carry out ω-lauric acid hydroxylation, the same treatment resulted in upregulation of the activity in male Fisher 344 rats. However, another study reported that treatment of male Wistar rats with *S. abortus equi* LPS caused downregulation of CYP4A1 and 4A3 [106]. In mice, hepatic lauric acid ω-hydroxylation and Cyp4a10 mRNA levels are depressed by treatment with *E. coli* endotoxin [20,64,83,152]. Modulation of Cyp4a14 appears to be strain-dependent in mice with LPS downregulating levels in C57BL/6 J [64] but not in C3H strains [20].

Treatment of rats with the sterile irritants barium sulfate or celite upregulated CYP4A1 mRNA but did not affect either CYP4A2 or CYP4A3 [132]. Microsomes from rats with collagen-induced arthritis had higher lauric acid hydroxylation when compared to nonarthritis rats [88]. In contrast, DSS-induced colitis in mice downregulated Cyp4a10 and 4a14 mRNAs [20]. Muntane *et al*. [137] reported that the presence of carrageenan-induced granuloma in rat depressed CYP4A levels.

19.8.2 CYP4F

Unlike with CYP4As, relatively little is available on the modulation of CYP4Fs by either inflammation or infection. In mice infected with *C. rodentium*, Cyp4f15 mRNA was downregulated while Cyp4f18 was upregulated [63,64]. Treatment of rats with *E. coli* LPS suppressed CYP4F4 and 4F5 expression by 50% and 40%, respectively [153,154], whereas CYP4F5 mRNA was upregulated [153]. LPS from *S. abortus equi* also downregulated CYP4F4 in rat liver after 4 h [106]. In hepatocytes, LPS downregulated CYP2C11, 4F4, and 4F5 [154].

19.9 FLAVIN MONOOXYGENASES

Flavin-containing monooxygenases (FMOs, EC 1.14.13.8) oxygenate substrates with a soft nucleophile, usually nitrogen or sulfur. While in many respects FMOs are similar to P450s and have overlapping substrate specificities, they often yield distinct metabolites. In rats, LPS treatment evoked decreases in hepatic content of FMO1 mRNA and protein, as well as of FMO activities, and these effects were attenuated by inhibition of nitric oxide synthases, suggesting a role for NO in the effect [155]. LPS treatment of mice depressed hepatic FMO1, 3, and 5 mRNAs but did not affect FMO4 mRNA [1]. Mice infected with *C. rodentium* had downregulated levels of FMO1, 3, 4, and 5 [1], and the downregulation of FMO3 persisted for at least nine days after the infection was resolved. The oxidation of nicotine to nicotine-1′-*N*-oxide is catalyzed by FMOs [91], and this activity was not changed in rats with D-galactosamine-induced hepatitis, in

comparison with the controls, but was significantly decreased in thioacetamide-induced cirrhotic rats [91].

19.10 CONJUGATION ENZYMES

19.10.1 Uridine 5′-Diphospho-Glucuronosyltransferases

The UDP-glucuronosyl transferases (UGTs) are a superfamily of glycosyltransferases (EC 2.4.1.17) that catalyzes the glucuronidation reaction. Mammalian UGTs are divided into four families, UGT1, UGT2, UGT3, and UGT8.

In animals with bacterial or parasitic infections, UGTs were reported to be either downregulated or not affected. Carp infected with *L. monocytogenes*, mice infected with *Plasmodium berghei, P. chabaudi chabaudi,* or *S. mansoni* and pigs infected with *A. pleuropneumoniae* had UGT activity similar to uninfected animals [58,74,76,79]. On the contrary, *P. berghei* infected rats were reported to have depressed UGT activity [77,156,157]. Infection of mice with *C. rodentium* resulted in the downregulation of Ugt1a1, 1a9, and 2b5 mRNA but not Ugt1a2 or 1a6 in the liver [158].

The i.p. administration of LPS to rodents did not affect transcription of UGT1A2 and 1A6, but it downregulated Ugt1a1 and 1Aa9 in mice [158] and UGT1A1, 1A6, 2B1, and 2B6 in rats [159]. Turpentine administered intramuscularly to rats was reported to have no effect on 4-nitrophenol glucuronidation but downregulated hepatic UGT isoforms from the UGT1 and two families [160]. Analysis of mRNA extracted from liver tissue samples of patients with fibrosis revealed general downregulation for several UGT1A and UGT2B isoforms that reached statistical significance only for UGT1A4, 2B4, and 2B7 [161]. In the rat, carbon tetrachloride-induced cirrhosis upregulated UGT2B1 [162] but did not affect 4-nitrophenol conjugation by a perfused rat liver [163].

In rodents with induced cancer, the reported modulation of UGTs is varied. Rats with 2-acetylaminofluorane-induced liver preneoplastic nodules had upregulated mRNA [164], while mice injected with Engelbreth-Holm-Swarm sarcoma cells had normal levels of Ugt1a7 but reduced levels of Ugt2b5 [134].

19.10.2 Sulfotransferases (SULTs)

The sulfotransferases (SULTs) (EC 2.8.2) are a gene family of enzymes that catalyze the transfer of a sulfonate group (SO_3^-) from a donor molecule, 3′-phosphoadenosine 5′-phosphosulfate, to a variety of acceptor molecules in a process referred to as *sulfonation* or *sulfurylation*.

In the rat, parasitic infections have been reported both to upregulate [156] as well as downregulate [125,157] SULT activity, while the LP-BM5 retrovirus that causes murine leukemia did not cause significant differences in the recovered urinary acetaminophen sulfate between infected and uninfected mice [165]. Intraperitoneal injection, or the treatment of rodent perfused liver with LPS, has been reported to cause the down-regulation of several isoforms in the SULT1 and SULT2 families. In comparison to healthy individuals, SULT1A1 activity increased almost 10-fold in patients with hepatocellular carcinoma secondary to chronic hepatitis B virus infection [68]. Transgenic mice injected with Engelbreth-Holm-Swarm sarcoma cells had higher levels of SULT1A1 but depressed SULT2A1 protein levels [134].

19.10.3 Glutathione *S*-Transferases (GSTs)

The glutathione *S*-transferases (GSTs) (EC 2.5.1.18) are a superfamily of enzymes that catalyze the nucleophilic attack of the sulfur atom of glutathione on an electrophilic group on a variety of lipophilic compounds. On the basis of amino acid sequence similarities, six classes of cytosolic GSTs are recognized in mammalian organisms, namely, alpha, mu, omega, pi, sigma, theta, and zeta designated A, M, O, P, S, T, and Z, while mitochondrial GSTs are designated kappa (K).

In humans, patients suffering from *Plasmodium vivax* malaria had about half the overall GST activity of patients without malaria [166]. De-Oliveira *et al*. [76] reported that when mice were infected with either *Plasmodium chabaudi chabaudi* or *P. berghei,* the conjugation of glutathione to l-chloro-2,4-dinitrobenzene (CDNB) in mouse liver did not change. All cytosolic GSTs, except class Theta are able to carry out this reaction. Infection with *Plasmodium yoelii nigeriensis,* on the other hand, reduced CDNB conjugation [167], while infection with *Angiostrongylus cantonensis* upregulated this activity [168].

Infection with hepatitis C virus (HCV) has been reported to upregulate levels of GSTA to over 150% when compared to HCV negative healthy subjects [169,170]. Viral infection of mice (hepatitis B or C) generally causes the upregulation of GST activity [66,169–171]. While the treatment of both F111 rat fibroblasts and human hepatoblastoma (HepG2) cells with SV40T antigen did not affect the GST levels as measured by Northern blotting, infection of HepG2 cells with the hepatitis B virus resulted in downregulation of GSTA [171].

The i.p. administration of up to 2 mg/kg *E. coli* endotoxin (LPS) has been reported to elicit no significant changes in mouse [145], juvenile carp (*C. carpio*) [87], or rat [111] GSTs. Choi and Kim [172] reported that i.v. LPS treatment downregulated GSTA and GSTM classes in rat liver. Endotoxin from *Salmonella typhimurium* and *S. abortus equi* have also been documented to reduce the expression or protein levels of GSTs in the A, M, and K classes [105,106,173] in rat liver.

19.10.4 Arylamine *N*-Acetyltransferases (NATs)

N-acetyltransferases (NATs) (EC 2.3.1.5) are enzymes that catalyze the transfer of an acetyl group from acetyl-CoA to an aromatic or heterocyclic amine, hydrazine, hydrazide, or *N*-hydroxylamine acceptor substrate. Humans have two isoforms, NAT1 and NAT2, while rodents have a third, Nat3 [174]. Compared with age and sex-matched healthy volunteers, HIV-infected subjects had 53% lower NAT2 activity [3].

19.11 EXTRAHEPATIC METABOLISM

19.11.1 Intestine

The intestinal P450 profile differs from that of the liver and shows large interindividual variation in the expression levels of individual P450s. CYP3A and CYP2C9 are the major intestinal P450s in humans, on average accounting for 80% and 15%, respectively [175]. The small intestine is the first site to metabolize orally ingested xenobiotics. Intestine-specific ablation of cytochrome P450 reductase in mice demonstrated that P450-catalyzed nifedipine metabolism in the small intestine plays an important role in the first-pass clearance of the nifedipine, and possibly other drugs [176].

CYP3A, P-glycoprotein (PGP) (mdr1), and MRP2 are important barriers to the absorption of many clinically important drugs in the intestine [177]. In the duodenums of pediatric patients with Crohn's disease, CYP3A mRNAs were higher compared with control groups [178]. Consistent with these observations, in a trinitrobenzenesulfonic acid model of colitis, rat colonic tissue samples showed increased activities of PGP-related efflux and CYP3A-catalyzed metabolism *ex vivo*. However, no change was observed in CYP3A metabolic activity and expression in the respective microsomal fractions [179]. The author suggested that increased metabolism could be due to infiltrating cells at the inflammation site [179]. Greer *et al*. studied the levels of nuclear receptors (NRs) and DME mRNAs in duodenum and colon biopsies of dogs with naturally occurring IBD or food responsive diarrhea (FRD) compared with healthy animals. In the duodenum, peroxisome proliferator-activated receptor-γ (PPARγ), constitutive androstane receptor (CAR), pregnane X receptor (PXR), and retinoid X receptor-α (RXRα) mRNAs were not different in any of the groups, while PPARα was elevated in colon only. Duodenal MRP2, CYP3A12, and SULT1A1 mRNAs were elevated in both FRD and IBD, whereas MDR1 mRNA was only elevated in FRD [180].

MDR1, MRP2, and CYP3A mRNAs were decreased by 50%, and CYP3A-mediated metabolism of 7- amiodarone and 7-benzyloxyquinoline were also decreased by ∼50% in the jejunum of LPS-treated rats [177,181]. The activity of PGP and CYP3A was also downregulated [181].

19.11.2 Lung

In human lung, CYP1A1 (in smokers), CYP1B1, CYP2B6, CYP2E1, CYP2J2, and CYP3A5 proteins are all expressed, as well as FMO and phase II conjugating enzymes [182]. Somers *et al*. [183] compared the expression and metabolizing activities of phases I and II enzymes in freshly isolated human lung parenchymal cells and cryopreserved human hepatocytes, showing that P450 gene expression and activities were generally lower in lung than in liver, whereas expression of all sulfotransferase isoforms in lung was similar to or higher than that in liver.

Rat pulmonary CYP1A and CYP2B1 activities were reduced by 3- and 1.5-fold, respectively 24 h after administration of LPS, while LPS had no effect on basal GST activity in both lung and kidney [184]. Levels of Cyp4a12 mRNA, the only detectible Cyp4a in mouse lung, were enhanced by fourfold in animals injected with IL- 1β [185]. During the acute inflammatory phase of ovalbumin-induced allergic airway disease the pulmonary mRNA levels of Cyp2e1, Cyp2f2, Cyp2j6, Cyp4b1, and Cyp8a1 were decreased while the mRNA levels of Cyp4f18, Cyp5a1, and Cyp7b1 were elevated [186].

19.11.3 Kidney

The highest concentrations of P450 enzymes in the kidney are found in the S_3 segment of the proximal tubules in the renal cortex [187]. LPS treatment caused the induction of renal CYP4A mRNAs in both rats [132,188] and SV/129 mice [152]. In contrast, LPS injection decreased renal CYP 4A1 and CYP 4A activity 4 h after injection in rat [189].

Anwar-Mohamed *et al*. reported that LPS injection was associated with the downregulation of CYP1A1, 1B1, 2C11, and 2J3 mRNAs in rat kidneys and hearts [188].

These authors also reported that CYP4F1, 4F4, and 4F5 were downregulated in the kidney, whereas Kalsotra *et al*. previously found no change of CYP4F1, 4F5, and 4F6 after LPS treatment [153]. The downregulation of the CYPs involved in arachidonic acid epoxygenation (2 C11 and 2 J2) was accompanied by a concomitant decrease in epoxyeicosatrienoic acids produced by these enzymes [188].

CYP2E1-mediated chlorzoxazone-6-hydroxylase activity and CYP2E1 mRNA and protein levels, as well as mRNAs of CYP4A2 and 4A3 were increased in rat kidneys 48 h after treatment with the particulate irritants SiO_2, $BaSO_4$, and kaolin [132]. $BaSO_4$ also induced renal CYP4F1 and 4F6 expression [153].

Infection with *C. rodentium* did not affect renal expression of most P450 isoforms (Cyp1a2, 2a5, 2c29, 2e1, 3a11, and 3a13) in C3H/HeOuJ mice. However, renal Cyp4a10 and 4a14 mRNAs were significantly downregulated [190]. Renal UGT isoforms were also relatively unaffected, except for Ugt2b5 which was induced [158]. The oxidation of *trans*-diethylstilbestrol to diethylstilbestrol-4′,4′-quinone by P450 in microsomes of estrogen-induced kidney tumors of male hamsters was only 10–20% of the rate compared to control kidney microsomes [191]. Significantly, total P450 content of the tissue surrounding the tumors was also reduced compared to control tissue. In contrast, traumatic brain injury in rats resulted in an elevation of renal CYP1A and CYP4F levels measured 24 h and two weeks after injury [153].

19.11.4 Central Nervous System

CYPlA1, CYPlA2, CYP2B1, CYP2B2, and CYP2E1 proteins are detected in the rat and/or human brain [192], and CYP2C29, CYP2D4, CYP2E1, CYP4F, and CYP3A9/11/13 are known to be expressed in brain [193]. Recently, higher levels of expression of CYP3A43 were discovered in brain as compared to liver across different ethnic populations [194].

The i.c.v. injection of LPS has been employed as a model of CNS inflammation, as it produces a robust inflammatory response in the brain characterized by the activation of microglia and astrocytes and the induction of inflammatory cytokine (TNFα, IL-6, and IL-1β) production [18,195,196]. This causes downregulation of CYP1A proteins and associated ethoxyresorufin *O*-dealkylase (EROD) activity in the brain [196]; reduced EROD activity in the brain was also observed after systemic LPS injection [195].

In rats with inflicted traumatic brain injury, hippocampal expression of CYP4F4 and 4F5 is transiently elevated before being downregulated, and hippocampal CY4F proteins are reduced to 20% of control within 24 h [154]. At this time point, CYP4F1, CYP4F4, CYP4F5, and CYP4F6 are all substantially downregulated in the fontal and occipital lobes of the brain as well [197].

19.12 DRUG TRANSPORTERS

DTs play important roles in drug metabolism and disposition, and they can be classified into efflux and uptake transporters. The largest family of efflux transporters is the ATP-binding-cassette (ABC) family, which are involved in the cellular efflux of many clinically important drugs. The family of uptake solute carriers (SLCs) also plays a central role in the cellular trafficking of numerous drugs [198].

Among the ABC drug efflux transporters, PGP/ABCB1, which is encoded by the multidrug resistance gene *MDR1* in humans and *MDR1a* and *MDR1b* in rodents, multidrug resistance-associated proteins (MRP1–3/ABCC1–3), and breast cancer resistance protein (BCRP/ABCG2) have particularly important roles in clinical drug disposition [198]. These transporters are highly expressed in epithelia of the intestine, liver, kidney, placenta, and blood–brain barrier, and they display a great deal of substrate overlap [198]. In addition, PGP, BCRP, and MDRs are known for their involvement in the extrusion of anticancer drugs from tumor cells and development of multidrug resistance. Members of the organic anion-transporting peptide (OATP, SLC21) family, especially OATP1 and OATP2, are important in the cellular uptake and oral bioavailability of a wide array of anionic drug substrates.

Inflammation also causes alterations in the expression and activity of DTs, contributing to changes in the absorption, distribution, and clearance of drugs and resulting in, for example, altered toxicity and compromised secretion of drugs into bile or urine [134,198]. Effects of inflammation on DT are described in a recent review by Teng and Piquette-Miller [199], and are summarized here in Table 19.5.

TABLE 19.5 Effect of LPS and Turpentine-Induced Inflammation on Various Drug Transporters

Transporter	Species	Tissue	LPS	Turpentine
MDR1a	Mouse	Liver	↓	↓
	Rat	Liver	↓	↓
	Rat	Intestine	—	↓
	Rat	Brain	↓	—
	Rat	Heart	↓	—
	Rat	Placenta	—	↓
MDR1b	Mouse	Liver	↓	↓
	Rat	Liver	↑	—
		Intestine	—	↔
	Rat	Placenta	—	↓
	Rat	Kidney	↔	—
ABCC1 (MRP1)	Rat	Brain	↓	—
		Placenta	↓	—
MDR2	Mouse	Liver	↓	—
	Rat	Liver	↓	—
MRP2	Mouse	Liver	↓	↓
	Rat	Liver	↓	
	Rat	Intestine	—	↓
MRP3	Mouse	Liver	↓	↓
	Rat	Intestine	—	↔
OATP2	Mouse	Liver	↓	↓
	Rat	Liver	↓	—
OATP4	Mouse	Liver	↓	—
BSEP	Mouse	Liver	↓	↓
NTCP	Mouse	Liver	↓	↓
	Rat	Liver	↓	—

Source: This table is adapted from the review article by Teng and Piquette-Miller [199].

19.12.1 LPS Model

As described above, LPS injection is a classic model of the inflammatory response, triggering the release of the proinflammatory cytokines IL-6, IL-1β, and TNFα and eliciting numerous changes in hepatic DMEs and DTs. In rats, hepatic mRNAs of MRP2, MRP6, OATP1, OATP2, OATP4, sodium taurocholate cotransporting polypeptide (NTCP), bile salt export pump (BSEP), organic cation transporter (OCT)1, and OAT3 were dramatically and rapidly downregulated following injection of LPS. In contrast, the efflux transporter mRNAs MRP1, MRP3, and MDR1b were induced; and MRP5 and OAT2 were unaffected [200]. LPS injection in mice results in mRNA downregulation of many hepatic DTs including Mdr1a, Mdr1b, Mdr2, Mrp2, Mrp6, Oatp1, Oatp2, Oatp4, Bsep, and Ntcp [198,201]; whereas, Mrp1 and Mrp5 are induced [201]. Note that Mdr1b mRNA levels are decreased in mice and increased in rats. Nevertheless, in both species decreased hepatic PGP protein expression is seen [202–204]. The effects of LPS on transporter expression were similar in wild-type (WT) C57BL6/J mice and in mice null for TNFα-receptor 1, IL-1 receptor, IL-6 or inhibitor of κB kinase β (IKKβ) [201].

19.12.2 Sterile Inflammation

Injection of the TLR2 agonist lipotechoic acid caused a transient downregulation of Mrp2 mRNA in mouse liver, whereas Mdr1b was induced and Mrp3 was unaffected [107]. Initial studies detected decreases of 50–70% in the hepatic expression and activity of PGP within 24–48 h after administration of turpentine [205]. These reductions, which occurred at the level of mRNA, were shown to stem from suppression of MDR1a and MDR1b nuclear gene transcription in turpentine-treated rats [206]. The effects of turpentine on hepatic transporter expression in mice are well summarized by Teng and Piquette-Miller: Mdr1a, Mdr1b, Mrp2, Mrp3, Oatp2, Bsep, and Ntcp are all downregulated [207].

19.12.3 Viral Infection

Nakai and coworkers studied the hepatic expression of CYP enzymes and DTs in chronic hepatitis C patients. They found that relative mRNA levels of CYP3A4 and OATP-C all were substantially downregulated compared to non-HCV livers. This correlated with the stage of fibrosis but not with inflammation [208]. CYP 1A2, 2E1, NTCP, and OCT1 were apparently elevated in the F1 stage of fibrosis, and then declined back toward normal levels as fibrosis progressed [208].

Treatment of rats with the TLR3 ligand poly I:C resulted in elevated plasma concentrations of IFNγ, TNFα, and IL-6, and significant downregulation of hepatic MRP2, BCRP, SLCO1A4, and SLC10A1 mRNAs; whereas MDR1b and MRP3 mRNA levels were significantly induced. Hepatic PGP, MRP2, and BCRP were significantly downregulated at the protein level. Many placental transporter mRNAs were also downregulated [146].

19.12.4 Other Inflammatory Diseases

Cholestasis in mice caused by bile duct ligation caused a downregulation of hepatic Oatp1 and induction of Mrps 1, 3, and 5. In the same model Oatps 2, 4, 5, 9, 11,

12, and 14; Mrps 1, 2, 4, 6, 7, and 9; and Ntcp and Bsep were unaffected [201]. The changes in DT expression were similar in mice lacking the genes for TNFα-receptor 1, IL-1 receptor, IL-6, or IKKβ, suggesting that compensatory or redundant mechanisms exist for this regulation [201]. In another model, mice inoculated with rotavirus (which causes intrahepatic cholestasis) had a downregulation of canalicular and basolateral hepatobiliary DTs and their regulatory NRs and a concomitant increase in inflammatory cytokines [209].

Several hepatic DTs, as well as CYP enzymes, are altered in animal models of end-stage renal disease (ESRD) [210–212]. For example, PGP is induced in the liver while OATP2 is downregulated. However, the possible contribution of inflammation to these effects is unknown, and uremic mediators may be responsible [211]. Diabetes is another disease with a strong inflammatory component. Streptozotocin-induced diabetic rats display decreased levels of MDR1a, MRP2, and BCRP and increased levels of MDR3 [213].

19.12.5 Regulation in Extrahepatic Tissues

Inflammation affects DT expression in the intestine, and can potentially affect drug absorption and oral bioavailability [198]. The mRNA and protein expression of PGP/MDR1a, MRP2, and CYP3A are downregulated by approximately 50% in the jejunum of LPS-treated rats [177]. The functional effects of these changes on absorption of PGP and MRP2 substrates were demonstrated in intestinal sections isolated from control and LPS-treated rats [177]. In the DSS model of colitis, mice have reduced expression of Mdr1a mRNA and PGP and PXR proteins in their large intestines [214]. In patients with active ulcerative colitis, mRNA and protein levels of BCRP and PGP were significantly reduced in the colons and rectums of individuals with active ulcerative colitis compared with controls or patients in remission, and were negatively correlated with the levels of IL-6 mRNA [215]. MRP2 mRNA, protein, or activity are decreased in the intestine of LPS-treated rats and in several other models of inflammation, including cholestasis and chronic renal failure [198].

PGP is expressed abundantly in several cell types within the CNS [198]. LPS-induced downregulation of PGP/MDR1a in brain tissues has been found to increase intracranial drug accumulation in rodents. Downregulation of PGP protein following i.v. LPS treatment was associated with increased accumulation of doxorubicin in mouse brains [216]. The i.c.v. LPS also downregulated CNS levels of PGP, Oatp2, and Mdr1a mRNAs, accompanied by elevated brain levels of the PGP substrate digoxin [204], demonstrating that localized CNS inflammation produces a loss of PGP function in the blood–brain barrier. The reduction of brain Mdr1a expression was blocked in mice with mutated TLR4, confirming that the activation of TLR4 receptor signaling is the major pathway involved in the reduction of brain Mdr1a expression [134].

Likewise, systemic and CNS inflammation produced by i.p. or intracranial administration of LPS triggered significant decreases in the expression of MDR1a mRNA in rat brain with analogous increases in the brain accumulation of PGP substrates such as ^{99m}Tc-sestamibi and digoxin [198]. Similar to liver, inflammation also resulted in a pronounced decrease of OATP2 in brain [204]. While hepatic mRNA levels of all Mdr isoforms are reduced in LPS-treated mice, Hartmann *et al*. reported that Mdr1b levels

are increased in kidney [217]. However, another study showed decreased renal expression of Mdr1a and Mdr1b mRNA [218]. Further studies are needed to understand the renal regulation of DTs respect to inflammation.

19.13 ROLES OF CYTOKINES

19.13.1 IL-1, TNFα, IL-6, and IFNs

Most investigations of the roles of cytokines in the regulation of DMEs and DTs have focused on IL-1, TNFα, and IL-6, as they are the major proinflammatory cytokines regulating hepatic acute-phase genes. IFNs have been studied because viral infections trigger the production of IFNs, and because IFN inducers can mimic the effects of viral infection on the P450 system [219]. Cytokines administered *in vivo* or incubated with cultured hepatocytes have enzyme-selective effects on CYP expression, and cultured hepatocytes have served as good models for the *in vivo* effects of cytokines [8,219–221].

IL-1, TNFα, and IL-6 as well as IFNs are capable of downregulating basal and drug-induced expression of many different CYP enzymes in cultured human and animal hepatocytes. For example, 72 h of IL-6, IL-1β, or TNFα treatment resulted in downregulation of mRNA levels and enzyme activities of CYP1A2, CYP2C, CYP2E1, and CYP3A in human hepatocytes [222]. More recently, we showed that, whereas CYP3A4 and CYP2C8 mRNAs were downregulated by IL-6, TNFα, IFNγ, or IL-1β in primary human hepatocytes within 24 h of treatment, other CYP2Cs and CYP2B6 showed cytokine-specific effects [8]. Of these cytokines, IL-6 downregulated the mRNAs of all CYPs tested except CYP2C18. Exposure of primary human hepatocytes to IFNγ resulted in downregulation of mRNA levels of influx transporters NTCP, OATP2B1, OATP1B1, and OATP1B3, as well as the efflux transporters MDR1, MRP2 protein, MRP3, BCRP, and BSEP [223].

In terms of inducible expression, IL-6, IL-1α, or TNFα treatment caused suppression of β-naphthoflavone-induced CYP1A1/2 mRNAs (with TNFα as the most potent) and of rifampicin-induced CYP3A4 mRNA (with IL-6 as the most potent) [224].

IL-1β, IL-6, TNFα, or IFNα all downregulated CYP2C11 mRNA in cultured rat hepatocytes. IL-6 was the most potent but least efficacious of these, and IFNγ had no effect [225]. However, IFNγ treatment did suppress both basal and induced CYP3A expression in rat hepatocytes [226]. Rat hepatocyte CYP4F5 is induced by IL-6, IL-1β, or TNFα treatment [227]. IL-10, an anti-inflammatory cytokine, suppressed CYP4F1, 4F4, and 4F5 expression [227].

IL-6, IL-1β, and TNFα suppress both P450- and UGT-dependent enzyme activities in primary pig hepatocytes, with IL-6 effects being slower than those of the other two cytokines [228]. IL-6 and TNFα produce stronger repression of CYP 1A1, 2 C8, and 3A4 in porcine hepatocytes than in human hepatocytes [229].

IL-β, TNFα, or IL-6 can also downregulate DTs in hepatocytes [230]. In primary human hepatocytes TNFα or IL-6 each caused the mRNA downregulation of influx transporters NTCP, OATP1B1, OATP1B3, OATP2B1, OCT1, and OAT2, and induced MRP3; whereas, IL-6 but not TNFα suppressed MDR1, MRP2, and BCRP [231]. On the other hand, IFNγ treatment downregulated mRNAs for NTCP, OATP 2B1, OATP1B1, and OATP1B3 as well as the drug efflux pumps MRP1, MRP2, MRP3, BCRP, and BSEP [223].

Many of the effects of cytokines on hepatocytes described above have also been observed when the same cytokines are administered *in vivo*, and this has been reviewed extensively [219]. For example, IFNγ administration to male rats suppressed CYP3A2 mRNA expression and activity [232]. IL-1 and/or TNFα administration resulted in the suppression of total P450 content, activities and/or P450 gene expression in rat and mouse liver [219]. Injection of IL-1β *in vivo* resulted in the suppression of rat female-specific CYP2C12 mRNA and protein [233], and also caused a decreased expression of CYP2C11 and CYP3A2, but not CYP2E1 in male rats [234]. TNFα administration causes the suppression of rat CYP3A2 and CYP2C11 mRNAs and proteins [235].

Administration of IL-6, IL-1β, or TNFα to mice has been shown to alter the expression of several DTs, especially via downregulation. These effects are summarized in Table 19.6, where a comparison of the impacts of cytokines on DTs in mice *in vivo* with those in cultured human hepatocytes reveals much commonality between the two model systems [199,230]. IL-1β, IL-6, and TNFα also caused differential effects on DT expression in human and murine hepatoma cell lines [199].

TABLE 19.6 Comparison of Cytokine Effects on Hepatic Transporter Expression in Mouse

	Liver and Human Hepatocytes		
Transporter	Cytokine	Mouse liver	Primary Human Hepatocytes
Mdr1a	IL−1β	↓	↓
	IL-6	↔	↓
	TNFα	↔	↔
Mdr1b	IL-1β	↔	—
	IL-6	↓	—
	TNFα	↑	—
Mdr2	IL-1β	↓	—
	IL-6	↓	—
	TNFα	↔	—
MRP2	IL-1β	↓	↓
	IL-6	↓	↓
	TNFα	↓	↔
MRP3	IL-1β	↔	↓
	IL-6	↔	↔
	TNFα	↓	↔
OATP2	IL-1β	↓	↓
	IL-6	↓	↓
	TNFα	↓	↓
BSEP	IL-1β	↓	↓
	IL-6	↓	↔
	TNFα	↔	↓
NTCP	IL-1β	↓	↓
	IL-6	↓, ↔	↓
	TNFα	↓	↓

Source: This table is adapted from the review articles of Teng and Piquette-Miller [199] and Fardel and Le Vée [230].

Most of the *in vivo* effects of cytokines on human drug metabolism have been observed with type I IFNs α or β, and these studies are well summarized in a recent review by Mahmood and Green [5]. The effects observed were highly variable and often contradictory. The response of DMEs to IFNs is obviously influenced by genetic, environmental, or other factors.

19.13.2 Other Cytokines

Data for cytokines other than the ones mentioned above is scant, and there is a need for more research in this area. The most information exists for IL-2, which is produced by T cells upon T-cell receptor activation, and functions in T-cell development and killer T-cell activation. Injection of IL-2 in rats modestly induced CYP2D mRNA and protein, as well as bufuralol demethylase activity. Several other microsomal drug metabolizing activities were also induced, whereas others were unaffected [236]. On the other hand, IL-2 treatment of cultured rat hepatocytes for 24 h was associated with downregulation of CYP3A2 and 2 C11 mRNAs as well as proteins of the 1A, 2B, 2 C, 2D, and 3A subfamilies [33], and these effects were attributed to increased expression of the transcription factor c-myc [237]. IL-2 receptor was identified on hepatocytes by immunofluorescence labeling. IL-2 also downregulated rifampicin induced, but not constitutive, CYP3A6 expression in cultured rabbit hepatocytes [238]. Patients with secondary hepatic cancer receiving treatment with IL-2 had reductions in the hepatic protein levels and activities of CYP1A2, CYP2C, CYP2E1, and CYP3A4 enzymes that were dependent on the IL-2 dose [239]. Cell culture studies revealed that IL-2 was able to downregulate CYP3A4 only when hepatocytes were cocultured with KCs [240]. Basiliximab and daclizumab are inhibitory anti-IL-2 receptor (a-chain) monoclonal antibodies approved by the FDA in 1998 to reduce organ transplant rejections. Daclizumab also tested successfully in a phase II trial for MS. Pediatric patients given basiliximab experienced high cyclosporine blood levels and toxicity [241]. This suggests that the antibody is countering an induction of CYP3A4 by IL-2, which is puzzling in view of the clinical observation of downregulation by IL-2 treatment [239].

IL-4 has important roles in T-cell development as well as in humoral and adaptive immunity. Its well-characterized targets are T cells and B cells. CYP2E1 mRNA was rapidly induced by IL-4 in human B16A2 hepatoma cells, which involved two independent signaling pathways: IRS1/2 via NFATc1 and a Stat6-dependent pathway [242]. In human hepatocytes, three days of IL-4 treatment induced the expression of CYP2E1 as well as GSTA1/2 mRNAs. [243], but the length of treatment may suggest an indirect effect.

IL-8 is a chemokine (chemotactic for neutrophils) and also has angiogenic activity. We found that IL-8 had no effect on the expression of CYP2C11 in rat hepatocytes, at concentrations up to 10 ng/mL [244]. However, IL-8 induces expression of the retinoic acid-catabolizing enzyme CYP26A1 in leukemia cells [245]. Since CYP26A1 contributes significantly to the hepatic clearance of the chemotherapeutic agent all-trans retinoic acid, its regulation in liver by IL-8 might be important to study [246].

IL-10 is a monocyte-derived cytokine that is considered to be anti-inflammatory, as it antagonizes many inflammatory pathways. However, when healthy humans were given 8 mg/kg IL-10 for six days, it evoked an APR characterized by reduced albumin and elevated ferritin in the serum [247]. CYP3A4-mediated midazolam clearance was

modestly inhibited by 12%, but there was no effect on CYP1A2-, 2D6-, or 2 C9-catalyzed drug clearance [247]. Another study found no effect of IL-10 treatment on the pharmacokinetics of prednisolone, a CYP3A4 substrate [248,249]. We found that IL-10 suppressed CYP4F1, 4F4, and 4F5 expression in rat hepatocytes [227].

IL-11 is a member of the IL-6 family of cytokines whose receptors dimerize with the gp130 protein to initiate cellular signaling. It is an inducer of APPs, and we showed that it also downregulates CYP2C11 mRNA in rat hepatocytes with an EC50 of ~100 pg/mL [244].

IL-17 is actually a family of highly related cytokines that are considered tobe proinflammatory due to their ability to stimulate cytokine production from many cell types. It induces the expression of the cholesterol-catabolizing enzyme CYP7B1 in synoviocytes, where it may be involved in maintenance of inflammation in rheumatoid arthritis [250]. The effects of IL-17 on liver or on drug metabolizing P450s are not known.

19.13.3 Knockout Mice

The aforementioned abilities of cytokines to downregulate P450s or DTs in hepatocyte model systems and in animals *in vivo* does not address their physiological importance. To address the question of what cytokines are important for the *in vivo* regulation of P450 isoforms and DTs caused by a given stimulus, cytokine null mice or cytokine receptor null mice have been used.

IL-6 is suggested to be the most important cytokine modulating the hepatic expression of APPs [84], and studies in IL-6-null mice also reveal it to be important in inflammatory regulation of P450 enzymes and DTs. Downregulation of Cyp1a2, Cyp2a5, and Cyp3a11 [84] and of Ntcp, Oatp1, Mrp3, Mrp2, and Bsep [251] mRNAs during turpentine-induced inflammation was abrogated in IL-6-deficient mice. IL-6-deficiency also blocked the downregulation of Cyp3a11 and 2c29 in mice treated with tuberculosis vaccine, while IL-1β gene deletion had no effect on Cyp3a11 or 2c29 downregulation in tuberculosis vaccine-treated mice [128]. We recently reported similar evidence for the involvement of IL-6 in the regulation of hepatic Cyp2d9, 3a11, and 3a13, in mice infected with *C. rodentium* [64], although the majority of CYPs were regulated in an IL-6-independent manner. These findings were in sharp contrast to those in the LPS model of inflammation, in which IL-6-null mice exhibited regulation similarly to WT of all the P450 enzymes [84] and DTs [201] that were studied. similarly in WT. IFNγ-null mice likewise had responses of hepatic P450s to LPS injection [64] similar to WT. Compared to WT, mice deficient in both TNFα receptors also had similar responses of P450 enzymes and activities to LPS [104]. Overall, the above results suggest a functional redundancy of cytokines during LPS-induced inflammation [84], such that the absence of any one will not greatly affect the regulation of DMEs or DTs.

19.13.4 Anti-Cytokine Antibodies and Biologic Drugs

One of the disadvantages of knockout mouse models is the possibility of compensatory mechanism developing over time. An alternative approach is to administer neutralizing antibodies to the cytokine in question. Ling and Jamali used this strategy to demonstrate the importance of TNFα to downregulation of CYP1A and CYP3A proteins. The therapeutic TNFα antibody infliximab partially inhibited the downregulation of these proteins in a rat model of adjuvant arthritis [7]. Similarly, in a different rat model

of rheumatoid arthritis, Ashino *et al*. demonstrated that polyclonal antibodies to IL-6 reversed the downregulation of CYP3A mRNA, protein and activity in the liver [6]. The fact that both TNFα and IL-6 seem to be involved in downregulation of CYP3As in arthritis probably reflects the fact that these cytokines can regulate each other's production. These observations in rats are proof of principle for the DDDIs discussed in Section 19.2.3. One such possible interaction for IL-2 is suggested by the study described in Section 19.13.2

19.14 MECHANISMS OF REGULATION

As described above, proinflammatory cytokines are thought to mediate most of the effects of inflammation on hepatic DME and DTs. Consequently, most mechanistic studies have focused on the effects of individual cytokines. Because cytokines exert enzyme-selective effects on P450 gene products, it is important to recognize that no single common pathway has been identified that is responsible for the downregulation of DMEs and DTs. Different mechanisms are likely to pertain depending on the specific gene and inflammatory stimulus and also on the time point in the response.

19.14.1 Transcriptional Regulation

In rat liver, 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 [252]. The swiftness and size of these effects suggest that transcriptional suppression is the primary mechanism for the decline of CYP mRNAs.

During an LPS-induced APR, mediated primarily by LPS and proinflammatory cytokines, the expression and activation states of many hepatic transcription factors change [253]. It must be recognized that the transcription factors that predominate in basal and drug-induced expression of DMEs and DTs are different, and that therefore the mechanisms of transcriptional downregulation will also be different between the two states [221].

The transcription factor NF-κB, a major regulator of inflammation, can be activated by many stimuli including cytokines via their receptor-associated kinases [254], viruses, oxidative stress, and chemical agents [255,256]. NF-κB has been implicated in the regulation of P450s via several different effects on their induction mechanisms [256,257]. The first mechanism is that NF-κB can regulate NR-mediated, inducible DME gene expression indirectly by suppressing expression of NRs and/or modulating their binding partner (e.g., RXR). For example, hepatic CAR and RXR expression is repressed in LPS-treated mouse liver [258], and IL-6 stimulation causes a reduction of PXR expression in primary human hepatocytes [259]. IL-1β decreases CAR expression and decreases phenobarbital-mediated induction of CYP2B6, CYP2C9, CYP3A4, UGT1A1, GSTA1, GSTA2, and SLC21A6 messenger RNA through chromatin remodeling by glucocorticoid receptor (GR)/NF-κB interaction [260]. NF-κB can interact with GR, PPAR, RXR, or farnesoid X receptor (FXR) [256].

The NF-κB pathway can also interact directly with NRs governing DMEs and DT expression [256,257]. Thus, inflammatory stimuli can suppress the induction of CYP3A4 by binding of the NF-κB p65 subunit to RXR, inhibiting PXR-RXR binding

to CYP3A4 promoter [261]. Inflammatory stimuli can regulate aryl hydrocarbon receptor (AhR) regulated genes (*CYP1A1, IA2*, and 1*B*1). NF-κB binds to AhR, and these two transcription factors can mutually repress each other's functions [262].

We found that NF-κB plays a role in the downregulation of CYP2C11 in rat hepatocytes in response to LPS or IL-1β, through direct binding to a negative response element spanning the transcription start site of the *CYP2C11* gene [263]. NF-κB binding can also be identified to the promoter regions of the *CYP1A1, CYP2B1/2, CYP2C11*, and *CYP2D5* genes by electrophoretic mobility shift assay (EMSA) [256], although this binding has not been shown to be functional.

IL-6 causes a moderate induction of the mRNA of the transcription factor CCAAT-enhancer binding protein-β (C/EBPβ, enriched in liver). However, a marked increase in the translation of a C/EBPβ isoform lacking a transactivation domain resulted in downregulation of CYP3A4 mRNA in hepatoma cells [264]. C/EBP binding to the promoter regions of CYP2D5 and CYP2B1 measured by EMSA is increased by LPS-induced CNS inflammation, suggesting that C/EBP could negatively regulate the gene expression of CYP2B1 and 2D5 [265].

Hepatocyte nuclear factors (HNFs) regulate the basal transcription of many CYP genes, and many of these factors are downregulated in inflammation [253]. DNA binding activities of HNF1α, HNF3β, and HNF4α are all rapidly suppressed in the rat liver following LPS treatment [252]. Therefore, it is likely that downregulation of HNF expression or activities during inflammation could contribute to the regulation of DME and DT expression [221]. Downregulation of HNF1α by LPS administration appears to contribute to the downregulations of CYP27A [266], NTCP [267], and OATP4 [268].

The question of whether downregulation or antagonism of NRs responsible for the induction of DMEs and DTs is also a mechanism for the downregulation of basal DME and DT expression is still open to debate. On the one hand, the phenotypes of PXR and CAR-knockout mice suggest little importance of these receptors in basal DME expression. In agreement with this idea, we found that LPS treatment downregulates hepatic P450 expression to a similar extent in PPARα or PXR-null mice compared to WT [83], indicating that downregulation of P450 during inflammation does not require PPARα and PXR. On the other hand, siRNA-mediated knockdown of PXR attenuates downregulation of CYP3A4 in human hepatocytes [269]. This could reflect a species difference in the role of PXR in basal P450 expression.

19.14.2 Posttranscriptional Regulation

As detailed in a previous review [219], there is an abundance of kinetic evidence that posttranscriptional mechanisms such as regulation of RNA degradation, protein synthesis, and protein degradation also function in the inflammatory regulation of DMEs and DTs. As a recent example, hepatic CYP2E1 mRNA was rapidly induced in the livers of rats treated with LPS via the i.p. or i.c.v. routes, and this induction persisted for 24 h, during which period the CYP2E1 protein was downregulated [140]. The mechanism of this posttranscriptional regulation is not clear.

Nitric oxide (NO) is a short-lived free radical produced during inflammatory and infectious conditions. We have shown that in cultured hepatocytes, NO formed by inducible nitric oxide synthase in response to an inflammatory stimulus causes a post-transcriptional downregulation of rat CYP2B [270] and CYP3A [271], as well as human CYP2B6 proteins [272]. For the rat CYP2B and CYP3A enzymes this is due to

increased proteasomal degradation of the enzymes [271]. In addition, NO can inhibit the activities of P450 enzymes by coordination to the P450 heme [221]. The *in vivo* relevance of these NO-dependent mechanisms has yet to be established.

19.15 CONCLUSIONS AND FUTURE PERSPECTIVES

The data from animal studies and the limited experiments in humans demonstrate that drug metabolism and transport can be profoundly affected in either direction in inflammatory disease states, and crucially, that this regulation depends on both the nature of the disease/inflammatory stimulus as well as on the specific protein in question. Much more research is needed into the regulation of DMEs and DTs in humans in specific inflammatory disease states, including diseases such as diabetes that have a chronic inflammatory component, and also into identification of biomarkers that can predict these changes. This will require not only clinical research in humans, but also mechanistic research in animal and cell culture models to identify blood-borne mediators, receptors, and signaling mechanisms involved. The effects of many cytokines on drug metabolism and transport have yet to be studied, as have the roles of noncytokine mediators and NLRs.

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