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Clinical and Molecular Perspectives on Inflammation-Mediated Regulation of Drug Metabolism and Transport

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Title: Clinical and Molecular Perspectives on Inflammation-Mediated Regulation of Drug Metabolism and Transport

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Abstract

Inflammation is a possible cause of variability in drug response and toxicity due to altered regulation in drug-metabolizing enzymes and transporters (DMETs) in humans. Here, we evaluate the clinical and in vitro evidence on inflammation-mediated modulation of DMETs, and the impact on drug metabolism in humans. Furthermore, we identify and discuss the gaps in our current knowledge. A systematic literature search on PubMed, Embase, and grey literature was performed in the period of February to September 2020. A total of 203 papers was included. In vitro studies in primary human hepatocytes revealed strong evidence that CYP3A4 is strongly downregulated by inflammatory cytokines IL-6 and IL-1β. CYP1A2, CYP2C9, CYP2C19, and CYP2D6 were downregulated to a lesser extent. In clinical studies, acute and chronic inflammatory diseases were observed to cause downregulation of CYP enzymes in a similar pattern. However, there is no clear correlation between in vitro studies and clinical studies, mainly since most in vitro studies use supraphysiological cytokine doses. Moreover, clinical studies demonstrate considerable variability in terms of methodology and inconsistencies in evaluation of the inflammatory state. In conclusion, we find inflammation and pro-inflammatory cytokines to be important factors in regulation of drug-metabolizing enzymes and transporters. The observed downregulation is clinically relevant, and we emphasize caution when treating patients in an inflammatory state with narrow therapeutic index drugs. Further research is needed to identify the full extent of inflammation-mediated changes in DMETs and to further support personalized medicine.

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1 Background

Pharmacokinetic variability causes altered drug response and toxicity within a population. The sources of variability may be caused by individual (e.g. comorbidity), environmental (e.g. drug-drug interactions (DDIs)), or genetic (e.g. poor metabolizers) effects on drug-metabolizing enzymes and transporters (DMETs). Identifying factors that contribute to variability in DMETs is crucial to predict drug response and toxicity.

Cytochrome P450 (CYP) enzymes play the most important role in the metabolism of numerous drugs, xenobiotics, and endogenous substances. The main CYP enzymes involved in hepatic drug metabolism are CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (1). Influx and efflux transporters in the liver contribute to hepatic uptake and elimination, while these transporters in the intestine are part of the absorption process of several drugs (2). Organic anion transporting polypeptide (OATP) 1B1 and 1B3, organic cation transporter 1 (OCT1), and organic anion transporter 2 (OAT2) are the main uptake transporters in the sinusoidal membranes of the liver, while P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2) contribute to biliary clearance of drugs and restrict drug absorption in the small intestine.

Inflammation has been identified as a possible factor contributing to regulation and variability of DMETs in humans (3–5). Inflammation is characterized by local and systemic release of cytokines and chemokines (6). Surgery, severe physical injury, or systemic bacterial or viral infections can cause acute release of pro-inflammatory cytokines, such as interleukin (IL) 6, IL-1β, and tumor necrosis factor alpha (TNF-α) (6,7). Similarly, chronic inflammatory diseases, such as rheumatoid arthritis and diabetes, are characterized by elevated systemic levels of these pro-inflammatory cytokines (6). The cellular mechanisms of cytokine-mediated regulation of DMETs are complex and involve multiple different signaling proteins and pathways. For example, IL-6 activates several pathways including the Janus Kinase and Signal Transducer and Activator of Transcription (JAK/STAT) pathway, Nuclear Factor-κB (NF-κB), and the Mitogen-Activated Protein Kinase and Extracellular signal-Regulated Kinase (MAPK/ERK) pathway (8,9). Therefore, individual cytokines and inflammatory diseases may affect the regulation of DMETs differently. The mechanisms of cytokine-mediated downregulation of the DMETs in human cells are described in

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detail elsewhere (10–14). Although several decades of research have sought to elucidate the significance of inflammation in modulating DMET expression and activity, the correlation between in vivo and in vitro studies remains to be established (3,10,15–17).

The increasing role of therapeutic antibodies for the treatment of various inflammatory diseases has led to new types of DDIs mediated by modulation of inflammatory cytokines in humans (18). Recently, The United States Food and Drug Administration (FDA) released a draft guideline focusing on the DDI assessment for therapeutic proteins outlining the emerging significance of these type of DDIs (19). Furthermore, recent literature contains several examples of clinically relevant DDIs mediated by therapeutic proteins (20–22). The research on DDIs between therapeutic proteins and small molecule drugs also improves the understanding of inflammation and cytokine-mediated regulation of DMETs.

In this review, we systematically evaluate the clinical and in vitro evidence on inflammation-mediated modulation of DMETs and subsequent impact on drug metabolism in humans. Clinical DDI studies with therapeutic proteins targeting cytokines are also included in our review as they provide indirect evidence of cytokine-induced regulation of DMETs. Although numerous animal studies on this topic are available, the findings from such studies may not translate to humans because of species differences. Thus, we focus exclusively on original research from human in vitro systems and clinical studies. Finally, we identify gaps in our current understanding of the impact of inflammation on the regulation of DMETs and ultimately, the pharmacokinetics of drugs.

2 Methods

We performed a systematic search of the literature in PubMed and Embase from the earliest record to February 27th, 2020. An updated search was performed on September 22nd, 2020. The search strategy was conducted using a combination of search terms, including inflammation (e.g., cytokines, interleukins, tumor necrosis factor, interferons, or c-reactive protein), drug metabolism (e.g., cytochrome P450, drug metabolizing enzymes, or drug transporters), interaction (e.g., enzyme

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activity, gene expression, or regulation), and human (e.g., patients, in vivo, in vitro, or hepatocyte). The full search strategy employed in this review is described in **Figure S1**.

Screening of title and abstracts was undertaken independently by two reviewers (A.D. and E.J.). After the initial screening, the full text of potentially eligible articles was assessed individually with A.D. focusing on clinical studies and E.J. focusing on in vitro studies. Any case of disagreement was resolved by discussion or by consulting a third reviewer (C.M.).

We excluded reviews, case reports, small case series, and conference abstracts. Citation tracking was performed in relevant publications to identify eligible studies missed by our search and relevant peer-reviewed publications. Specifically for therapeutic proteins, the Clinical Pharmacology Reviews at Drugs@FDA (www.FDA.gov) was consulted. Only reports in English were included. Additional inclusion and exclusion criteria are outlined below.

2.1 Selection of cell model studies and data extraction

We included original in vitro studies using human-originating cell lines or human primary cells. The inclusion criteria for the in vitro studies were: a) studies employing hepatic, intestinal, renal, and brain in vitro models; b) studies reporting data on mRNA expression, protein expression, or activity of drug-metabolizing enzymes and drug transporters; c) studies investigating single cytokines or chemokines or their combinations, but not combinations of cytokines with enzyme inducing drugs. We excluded studies containing exclusively animal data either in vivo or in vitro.

The complete data extracted from in vitro studies are reported in **Table S1.** No studies with renal cells were identified and only limited reports were available on primary brain endothelial or intestinal cell models (**Table S1**). In Results (section 3.1), only findings from primary human hepatocyte studies are reported and discussed, while the extracted data from studies in other cell models are reported in **Table S1**. Moreover, the findings reported here are limited to studies published after year 2000 to exclude older articles with possible outdated cell culture methodologies. Details of all studies identified, such as cell culture format or number of hepatocyte donors in each study, are listed in **Table S1**.

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2.2 Selection of clinical studies and data extraction

We included original clinical studies. The inclusion criteria for the clinical studies were: a) studies performed in an adult or pediatric population (age>1 year); b) studies reporting CYP enzyme or drug transporter activities, pharmacokinetics, or pharmacodynamics of drugs; c) studies assessing a specific inflammatory condition. We excluded studies assessing herbal medications, vitamins, inhaled particles, or enzymes primarily involved in the metabolism of endogenous substances. Additionally, we assessed the impact of therapeutic proteins on drug metabolism and transport. Only studies investigating direct cytokine agonists or antagonists were included, while therapeutic proteins affecting other steps of the inflammatory pathways were not taken into consideration.

Studies of biopsies obtained from patients with inflammatory diseases were included based on the same criteria as the in vitro studies (**Table S2**).

In Results (section 3.2), only findings from studies employing specific probe drugs are reported and discussed. Moreover, the findings reported here are limited to studies published after year 2000 to exclude older articles with possible poorer methodologies and unspecific probe drugs. Details of all studies identified are listed in **Table S5 and S6**. Only statistically significant differences were reported as differences. Generally, differences of 0.8-1.25-fold were considered within the bioequivalence and thereby negligible.

3 Results

A total of 203 references were included in our review with 78 articles based on in vitro data and 102 articles based on in vivo data. We included 33 articles analyzing biopsies from patients with inflammatory diseases (**Table S2**).

Studies in healthy subjects have shown considerable interindividual variability in serum concentrations of pro-inflammatory cytokines. However, the average concentrations (± Standard deviation) of the 4 most important cytokines in an elderly healthy population (>65 years) are: IL-6: 2.6 ± 5.2 pg/ml, IL-1β: 2.5 ± 7.4 pg/ml, TNF-α: 4.9 ± 4.8 pg/ml, and IFN-γ: 10.3 ± 18.4 pg/ml (23).

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3.1 Impact of pro-inflammatory cytokines on in vitro expression and activity of main drug-metabolizing CYP enzymes and drug transporters in primary human hepatocytes

We reviewed in vitro literature assessing the impact of pro-inflammatory cytokines on drug-metabolizing enzymes (section 3.1.1) and transporters (section 3.1.2) in primary human hepatocytes. Primary human hepatocytes are currently the gold standard to study the regulation of hepatic DMETs at the level of expression and activity, and thus we present only studies that utilize these cells. The sections below focus on the main hepatic CYP enzymes, efflux-, and uptake transporters involved in drug metabolism in humans. IL-6, IL-1β, TNF-α, and IFN-γ are covered in detail, while the summary of data available on other cytokines and chemokines are presented in **Table S3** for CYP enzymes and in **Table S4** for efflux and uptake transporters.

3.1.1 The effect of cytokines on the main CYP enzymes in primary human hepatocytes

We summarize the effect of specific cytokines on the main drug-metabolizing CYP enzymes in the liver CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 (1). Results on IL-6, IL-1β, TNF-α, and IFN-γ are summarized in **Tables 1 and 2**. The information on other drug-metabolizing enzymes from our literature search is available in **Table S1**.

3.1.1.1 Interleukin-6 (IL-6)

The in vitro effect of IL-6 on the mRNA expression of CYP enzymes in primary human hepatocytes have been reported in multiple studies (24–42). IL-6 substantially downregulates the mRNA expression of CYP3A4 up to 100-fold at 10 ng/ml (25–27,29–31,33–42), while other CYP enzymes are downregulated 1.5- to 8-fold by 10 ng/ml IL-6 (25–27,30,33,34,36–42). A study reported a 2-fold upregulation of CYP2D6 mRNA by IL-6 (33), however, two other studies reported a maximum of 2- to 3-fold downregulation of CYP2D6 mRNA at the same IL-6 concentration (32,36). The mRNA expression of CYP3A5 is also downregulated by IL-6 in primary human hepatocytes, but to a lower degree than CYP3A4 (32,36).

In line with the reduced expression of CYP enzymes, IL-6 leads to downregulation of CYP enzyme activity in primary human hepatocytes (24,26,28,31–37,39,40). CYP3A4 activity is markedly downregulated up to 50-fold by 10 ng/ml IL-6, while the enzyme activity of other CYP enzymes is downregulated 1.5- to 7-fold.

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Dose-response of IL-6 on the downregulation of CYP enzymes was investigated in a few studies (24,32,35,42). The concentrations resulting in half of the maximal suppression of expression are typically 100 pg/ml of IL-6 (**Table 2**), which is 100-fold lower than the concentration of 10 ng/ml IL-6 often employed in vitro (**Table 1**). For CYP3A4, IL-6 may suppress the mRNA expression at a concentration as low as 3 pg/ml (32). Three studies investigated the concentration-dependent effect of IL-6 on the enzyme activity of either CYP1A2 or CYP3A4 (24,32,35). The suppression of enzyme activities also occurs at low concentrations of IL-6, 70-374 pg/ml for CYP3A4 and 1,250 pg/ml for CYP1A2 (24,32,35). The maximal suppression found in these studies was 3- to 14-fold for CYP3A4 and 4-fold for CYP1A2. The concentration-dependent suppression of the enzyme activity of CYP3A4 by IL-6 was not changed in a co-culture of Kupffer cells together with hepatocytes in a micropatterned hepatocyte cell culture (35).

3.1.1.2 Interleukin 1β (IL-1β)

IL-1β suppresses the mRNA expression of CYP1A2, CYP2C8, CYP2C9, CYP2D6, and CYP3A4 in primary human hepatocytes, while the expression of CYP2B6 is not affected at concentrations of 5-10 ng/ml of IL-1β (25,35,43,44). The effect of 5-10 ng/ml IL-1β is strongest for CYP3A4 with 4- to 42-fold downregulation, while CYP1A2, CYP2C8, CYP2C9, and CYP2D6 are downregulated 2- to 5-fold (25,35,43,44). One study reported a 2-fold downregulation of CYP2C19, while another study found no effect of 5 ng/ml IL-1β on the expression of CYP2C19 (25,43). The mRNA expression of CYP3A5 is 2-fold downregulated by 10 ng/ml IL-1β (43).

The dose-response of IL-1β on the mRNA expression of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 indicates that IL-1β concentrations of 150-950 pg/ml results in half of the maximal suppression of these CYP enzymes (43). Similarly, the enzyme activity of CYP1A2 is suppressed to half by 450 pg/ml of IL-1β (43). The mRNA expression and enzyme activity of CYP3A4 are affected at lower concentrations of IL-1β as indicated by IC_{50} values of 10-400 pg/ml (35,43,44).

A study investigated synergistic effects of IL-1β and IL-6 at physiological relevant concentrations in hepatocytes from one donor. The IL-6-mediated downregulation of CYP1A2, CYP2B6, CYP2C9, and CYP3A4 was not affected by addition of IL-1β (43). Moreover, 100 pg/ml IL-1β did not downregulate the mRNA expression of CYP1A2, CYP2B6, and CYP2C9, or the mRNA expression and activity of CYP3A4. Another study found substantial downregulation of CYP3A4

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enzyme activity by IL-1β, with a IC_{50} value of 98 pg/ml, only in the presence of Kupffer cells together with hepatocytes in a micropatterned hepatocyte cell culture (35).

3.1.1.3 Tumor necrosis factor α (TNF-α)

Three studies have investigated the effect of 10 ng/ml TNF-α on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in primary human hepatocytes (25,30,33). TNF-α suppresses the mRNA expression of CYP1A2, CYP2C8, and CYP2D6 by 1.5- to 3-fold, while the expression of CYP3A4 is suppressed by 5- to 8-fold (25,30,33). CYP2B6, CYP2C9, and CYP2C19 are not affected by this cytokine (25,33). A study reported TNF-α suppressing the enzyme activity of CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4 by 1.5- to 7-fold, which is in line with the effect on the mRNA expression for all but CYP2C19 (33).

3.1.1.4 Interferon-γ (IFN- γ)

Only one study investigated the effect of IFN-γ on CYP expression in primary human hepatocytes (25). At 10 ng/ml of IFN-γ, the mRNA expression of CYP2B6 and CYP3A4 was downregulated 4-fold while CYP2C8, CYP2C9, and CYP2C19 were downregulated by 1.25- to 2-fold.

3.1.2 In vitro effects of cytokines on drug transporters

The hepatic uptake transporters OATP1B1, OATP1B3, OCT1, and OAT2 are downregulated by IL-6, IL-1β, and TNF-α at concentrations of 1-100 ng/ml in primary human hepatocytes (26,36,41,44–47). IFN-γ also downregulates OATP1B1 and OATP1B3 by 3-fold at 10 ng/ml, while OCT1 and OAT2 are not affected by this cytokine (47). The impact of IL-6, IL-1β, TNF-α, and IFN-γ on drug transporters expression is summarized in **Table 3**.

IL-6 downregulates OATP1B1, OATP1B3, and OCT1 by 2- to 42-fold at 10 ng/ml (26,36,41,46), while a concentration of 0.1 ng/ml does not affect the mRNA expressions and 1 ng/ml results only in a 2-fold decrease of OAT1B1 and OCT1 (46). Moreover, 10 ng/ml of IL-6 results in a 1.5-2-fold decrease of the OAT2 expression (36,46).

A study further characterized the concentration-dependent effect of IL-1β on the mRNA expression of OATP1B1, OATP1B3, OCT1, and OAT2 (44). The concentration resulting in half of the

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maximal suppression of the transporters was 16-36 pg/ml of IL-1β and the maximum effect was 3- to 7-fold downregulation (44).

Exposure of 1 ng/ml TNF-α results in 2-fold downregulation of OATP1B1, OATP1B3, OCT1, and OAT2, while a concentration of 0.1 ng/ml does not affect their expression (46).

Effect of IL-6, IL-1β, TNF-α, or IFN-γ, at concentrations of 1-100 ng/ml, on the mRNA expression of hepatic efflux transporters P-gp, MRP2, and BCRP is generally low with a maximum downregulation of 2-fold (26,36,38,44–46,48).

3.2 Impact of inflammation on in vivo activity of main drug metabolizing CYP enzymes and drug transporters in humans

We reviewed the literature for clinical studies assessing the impact of infection and inflammatory diseases on the activity of drug-metabolizing activity and transport. We address the literature on chronic inflammatory disease (section 3.2.1), effects of therapeutic proteins, targeting different inflammatory pathways, on drug metabolism of small-molecule drugs (section 3.2.2) and acute inflammatory disease (3.2.3).

In the following sections, we only present pharmacokinetic data from studies employing probe drugs for specific enzymes or transporters exemplified by, but not limited to, the ones included in the FDA guideline on Drug Development and Drug Interactions (49). Older references (before year 2000) and studies employing unspecific probe drugs are presented in **Table S5 and S6**.

3.2.1 Chronic inflammatory diseases

Chronic inflammatory diseases cover a wide range of conditions with varying degrees of inflammation. Among these diseases, the impact of rheumatoid arthritis on drug metabolism is the most well described. An overview of how chronic inflammatory diseases affect CYP enzymes are presented in **Table 4**.

Rheumatoid arthritis is an autoimmune disease characterized by joint destruction and systemic immune response. Most patients with rheumatoid arthritis experience increased plasma levels of IL-6 of 50 pg/ml (21,50,51), which is much higher than the level of 2.6 pg/ml found in healthy

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individuals (**section 3**). However, IL-6 levels as high as 140 pg/ml among patients have been reported (52). In a pharmacokinetic study of eight patients with rheumatoid arthritis, the AUC of verapamil (CYP3A4 substrate) was 4-fold higher compared to healthy individuals (52). The effect was similar for both enantiomers of verapamil. Patients with rheumatoid arthritis exhibited increased levels of IL-6 with mean plasma concentrations of 140 pg/ml which correlated to disease severity. Despite the increased verapamil exposure, patients experienced a paradoxical decrease in the pharmacodynamic effect on conduction velocity through the heart (52). A similar study (50) showed no significant differences in verapamil pharmacokinetics among 20 patients with rheumatoid arthritis in remission compared to healthy individuals (50). Similarly, a study assessed the activity of CYP2C9 in a study including 12 patients with controlled arthritis, 14 patients with active arthritis, and 12 healthy individuals. Following administration of a 100 mg single dose of losartan (CYP2C9 substrate), the AUC of the active metabolite EXP3174, was 1.8-fold and 2.8-fold lower in the controlled arthritis and active arthritis group, respectively (53). These results indicate that the CYP2C9 activity is decreased in patients with rheumatoid arthritis in a disease-activity specific manner.

As for transporters, single-dose valsartan (OATP, MRP2, and CYP2C9 substrate) pharmacokinetics did not differ between patients with active rheumatoid arthritis (n=14), patients with controlled arthritis (n=12) and healthy individuals (n=12) (54). On the contrary, a clinical pharmacokinetic study showed that the concentration of fluvastatin (OATP and CYP2C9 substrate) was higher in patients with rheumatoid arthritis under pharmacological treatment (n=10) compared to healthy individuals (n=15). Racemic fluvastatin was administered to both groups for 7 consecutive days, before measuring fluvastatin pharmacokinetics. The AUC of both enantiomers was 2.0- to 2.5-fold higher, and clearance was 2.0- to 2.5-fold lower in patients with rheumatoid arthritis compared to healthy individuals. Plasma concentrations of IL-6, IL-8, IL-10, MCP-1, and TNF-α were 1.5- to 2.5-fold higher in patients with rheumatoid arthritis compared to healthy individuals while there were no differences in IFN-γ and IL-1β concentrations (55).

Patients with psoriasis have substantially lower inflammation than rheumatoid arthritis with mean IL-6 plasma concentration of 4.2 pg/ml (56). Accordingly, the pharmacokinetics of a single dose of venlafaxine (CYP2D6 and CYP3A4 substrate) is not different in patients with psoriasis (n=13) compared to healthy individuals (n=11) (56).

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Two similarly designed studies in Turkish patients examined the impact of Behçet's disease on the activity of CYP2C9 and CYP2C19 (57,58). The mean losartan/E-3174 metabolic ratio was 2-fold higher in 52 patients with Behçet's disease compared to healthy controls (58). Similarly, the median lansoprazole/5-hydroxy lansoprazole metabolic ratio was 2.5-fold higher in 59 patients with Behçet's disease compared to healthy controls (57). This indicates a moderate downregulation of both CYP2C9 and CYP2C19 in patients with Behçet's disease.

Intestinal inflammatory diseases are associated with decreased activity of CYP3A4 and efflux transporters. Verapamil pharmacokinetics (CYP3A4 and P-gp substrate) was examined in a study of 14 patients with active Crohn's disease, 22 patients with Crohn's disease in remission and 22 healthy controls (59). The AUC of the two enantiomers was 2 to 8-fold higher in patients with active Crohn's compared to healthy controls. Despite the substantially increased plasma concentrations, no change in verapamil pharmacodynamics was observed (59). Similarly, another study found that the C_{max} of simvastatin (CYP3A4 and OATP substrate) was 2-fold higher in patients with active celiac disease (n=20) compared to healthy individuals (n=11). No difference in simvastatin C_{max} was found between patients with treated celiac disease (n=25) and healthy individuals (n=11) (60).
Several studies have investigated DMET expression in intestinal biopsies from patients with local intestinal inflammatory diseases e.g. ulcerative colitis and Crohn's diseases (**Table S2**) (61–65). Studies indicate that the mRNA and protein expression of CYP3A4, CYP2C9, CYP2C19, and CYP2B6 are downregulated and CYP2D6 is upregulated in intestinal biopsies from patients with intestinal inflammatory diseases. Additionally, the expression of the intestinal efflux transporters, P-gp and BCRP, are downregulated whereas the intestinal uptake transporter, OATP2B1, is upregulated in intestinal biopsies. Since intestinal inflammatory diseases are characterized by local inflammation, it might be difficult to extrapolate to other systemic inflammatory diseases. Nevertheless, the downregulation of intestinal transporters by local inflammatory disease might explain the alterations in systemic pharmacokinetics seen in the clinical trials of systemic inflammatory diseases like Crohn's disease (59).

The activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 was determined in 38 patients with type 2 diabetes and compared to 35 healthy individuals (66). To assess the individual CYP-enzymes, a drug cocktail consisting of caffeine, bupropion, tolbutamide,

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omeprazole, dextromethorphan, chlorzoxazone, and midazolam was administered to each participant. The study found that patients with type 2 diabetes had 2-fold decreased metabolic ratio for bupropion (CYP2B6 substrate) and omeprazole (CYP2C19 substrate), and a 1.5-fold decreased metabolic ratio for midazolam (CYP3A4 substrate), suggesting decreased activity of CYP2B6, CYP3A4, and CYP2C19 (66). The pharmacokinetics of the other probe drugs were unaffected (66). A study examined mRNA expression of CYP enzymes and transporters in duodenal biopsies from patients with type 2 diabetes and found no differences compared to controls (67).

Similarly, among 16 patients with congestive heart failure, a drug cocktail was administered, consisting of caffeine (CYP1A2), mephenytoin (CYP2C19), dextromethorphan (CYP2D6), and chlorzoxazone (CYP2E1) (68). The study revealed an inverse correlation between TNF-α and IL-6 concentrations and CYP2C19 activity. Median TNF-α and IL-6 concentrations were 4.8 pg/ml and 7.0 pg/ml, respectively. CYP1A2 activity increased with inflammation, while the activity of CYP2D6 and CYP2E1 was not altered (68). Cancer patients also exhibit low-grade-inflammatory state, but only CYP3A4 and CYP2E1 activity may be affected in these conditions (69,70). A study showed that tolbutamide clearance and metabolic ratio (CYP2C9) were similar in 10 patients with cancer compared to 10 healthy individuals (69). In another study of 22 females with advanced ovarian cancer, the metabolic ratio of chlorzoxazone (CYP2E1) and omeprazole (CYP3A4) was 3.5-fold higher and 2-fold lower, respectively, compared to healthy individuals. The activity of CYP1A2 (caffeine), CYP2D6 (dextromethorphan), and CYP2C19 (omeprazole) were not affected (70).

The impact of chronic HIV (human immunodeficiency virus) infection on CYP-metabolism and P-gp transport was assessed in two studies (71,72). In 17 HIV-infected individuals, midazolam clearance was 1.5-fold lower, and dextromethorphan/metabolite urinary ratio was 9-fold higher compared to healthy individuals, suggesting decreased activity of CYP3A4 and CYP2D6 in HIV. CYP1A2-mediated metabolism of caffeine was not affected (71). Another study compared the activity of CYP3A4, CYP2D6 and P-gp in 10 treatment-naïve HIV-infected patients compared to healthy individuals (72). CYP3A4 activity was 2-fold lower in patients with HIV assessed by oral midazolam clearance. However, administration of intravenous midazolam showed no differences between HIV-infected patients and healthy individuals, suggesting that mainly intestinal CYP3A4 is affected by HIV while hepatic CYP3A4 is unaffected. Similarly, P-gp activity was slightly lower

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in patients with HIV based on a 1.5-fold higher digoxin C_{max} but an unchanged AUC. CYP2D6 activity (dextromethorphan) was not affected (72).
In line with the results from clinical studies, a study assessed the mRNA expression of CYP3A4, BCRP, MRP2, and P-gp in jejunal biopsies from HIV-infected patients (73). Compared to biopsies from healthy individuals, the expression of CYP3A4, BCRP, and P-gp were 1.5- to 2-fold lower, while the expression of MRP2 was 4-fold lower.

In 14 patients with active chronic hepatitis C, the activity of CYP3A4 and CYP2D6 were 3-fold and 5-fold lower, respectively, compared to historic data from healthy individuals (74). Dextromethorphan was used as a probe drug to assess the activity of both CYP enzymes, based on different metabolites. No changes were seen in CYP1A2 activity assessed by caffeine drug/metabolite ratio (74). Contradictory results were found in another study, where midazolam pharmacokinetics (CYP3A4) was unaffected in 35 treatment-naïve patients with hepatitis C compared to healthy subjects (n=107) (75). However, the same study found a significant decrease of CYP3A4 activity in 24 patients with previous resistance to interferon therapy. This group had a 2-fold lower midazolam AUC_{last} compared to healthy subjects (n=107) (75).

3.2.2 Therapeutic proteins and their impact on drug metabolism

Therapeutic proteins have gained increasing interest during the past decades due to their potential to revolutionize the treatment of diseases. With this review, we only focus on therapeutic proteins directly linked to interleukins (ILs), interferons (IFNs), and tumor necrosis factor (TNF)-α, as presented in **Table 5**.
IFNs are indicated for malignant diseases, infections, and inflammatory diseases and act by supporting and enhancing an existing signaling pathway. The first recombinant IFN was produced in the 1980s. Likewise, the first reports of a potential drug-disease-drug interaction by IFNs were published in 1986. Since then, multiple studies have investigated the potential pharmacokinetic DDIs by IFN-α and -β, in both healthy individuals and patients (**Table S6**). A total of five studies have evaluated the impact of treatment with IFN-α or -β on CYP-enzyme activities. No changes in the activities of CYP3A4 and CYP2D6 (both dextromethorphan) or of CYP1A2 (caffeine) were observed in 14 patients with chronic hepatitis C following 1 month of treatment with IFN-α (74). On contrary, a study of 26 patients with chronic hepatitis found a 2-fold increase in CYP2D6 activity (dextromethorphan) following 4 weeks of IFN-α treatment. No changes were observed for

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CYP1A2 (caffeine), CYP2C8/9 (tolbutamide), or CYP3A4 (midazolam) (76). Similarly, in healthy individuals IFN-α treatment did not alter CYP enzyme activity (77). Accordingly, CYP2C19 (mephenytoin) or CYP2D6 (debrisoquine) activities were unaffected in 10 patients with multiple sclerosis following one month of IFN-β treatment (78).

IL-6 is an important mediator in the inflammatory response and plays a major role in both acute and chronic inflammation. In hepatocytes, IL-6 leads to activation of an intracellular signaling system and induce an acute phase response. The humanized IL-6 receptor antibody tocilizumab blocks this pathway and leads to an immediate decrease in CRP concentrations within 1-2 weeks of initiating treatment, to a level within the normal range (21,51,79). Furthermore, the regulation of CYP enzymes within hepatocytes is affected by the reduced IL-6-mediated signaling **(Figure 1)**. Two clinical pharmacokinetic trials investigated the impact of intravenous and subcutaneous administration of the IL-6 receptor inhibitors, tocilizumab and sarilumab, on the metabolism of simvastatin (CYP3A4 and OATP) (21,51). In these studies, 12 and 19 patients with rheumatoid arthritis were treated with a single dose of an IL-6 receptor antibody, which resulted in a decrease of mean simvastatin exposure (AUC_{last}) of 2-fold one week after the treatment (21,51). This effect persisted up to 5 weeks after tocilizumab infusion (51). In line with these results, a single dose of IL-6 inhibitor sirukumab was evaluated in 12 patients with rheumatoid arthritis (79). CYP3A4 and CYP2C19 activities were increased by 1.5-fold and 2-fold 1 week after the injection and persisted for 6 weeks. Alterations in CYP2C9 activity were within bioequivalence boundaries, while CYP1A2 activity decreased, resulting in an increase in caffeine AUC of 1.5-fold after sirukumab administration (79) **(Table 5)**.

Antibodies towards IL-2 (80), IL-4 (81), IL-17 (82), IL-17 receptor (83), and IL-23 (84–86) are used to treat inflammatory diseases. None of these have shown the ability to alter CYP enzyme activity in the relevant patient groups (**Table 5**). TNF-α (87,88) and the non-inflammatory cytokine IL-10 (89) have only been assessed in healthy individuals, without altering CYP or P-gp activity **(Table 5)**.

3.2.3 Acute inflammatory diseases

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Acute infectious disease is a common cause of systemic inflammation. Both viral, bacterial, or parasitic infections and acute tissue damage caused by sudden injury or surgery can induce systemic inflammation. The impact of these conditions on CYP enzymes is presented in **Table 4**. Among patients with head injury and undergoing surgery, the reported mean IL-6 concentrations are as high as 250-400 pg/ml (**Table S5**). For minor inflammatory diseases or infections, reports are limited to artificial inflammatory conditions induced by lipopolysaccharide (**Table S5**).

The body's most extreme response to infection is sepsis, a potentially life-threatening condition characterized by organ dysfunction. In a clinical pharmacokinetic trial, a single dose of 20 mg atorvastatin was administered orally to a cohort of 25 critically ill patients with sepsis. Plasma pharmacokinetics revealed an 18-fold higher C_{max} and a 15-fold higher $AUC_{0\text{-}24\ h}$ compared to healthy individuals (90). Atorvastatin is a substrate of OATP and CYP3A4, and both the transporter and enzyme are rate-limiting for the elimination of atorvastatin (90).

Two studies investigated the impact on CYP1A2 activity in hospitalized children with acute exacerbation of asthma (91) and adults undergoing cardiac surgery (92), respectively. Both studies employed theophylline as a probe drug and found theophylline plasma concentrations to be increased in the acute phase, suggesting decreased CYP1A2 activity (**Table 4**). However, theophylline metabolism is rate limited by renal elimination and the observed changes in theophylline metabolism might be explained by acute physiological alterations such as altered urine flow and hemodynamics.

In a study of 23 severely injured adults, of otherwise good general health, CYP enzyme activity was assessed. Mephenytoin (CYP2C19 substrate) and chlorzoxazone (CYP2E1 substrate) urinary recovery were decreased by 5-fold and 1.5-fold during the first week of hospitalization compared to healthy controls. This implies a profound suppression of CYP2C19 activity, and to a lesser extend CYP2E1 activity, following acute injury (93). In contrast, CYP2C9 activity increased within the first week after injury assessed by a 1.5-fold increase in the ratio of urinary recovery of flurbiprofen (CYP2C9 substrate) and metabolites. The activity of CYP2C19 and CYP2C9 remained decreased 2-4 weeks after injury, while CYP2E1 activity was normalized (93).

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Only a few studies have investigated the impact of intracellular parasitic protozoa infections on drug metabolism. The disposition of caffeine was assessed in 10 patients infected with the malaria parasite *plasmodium falciparum* and compared to 10 healthy individuals. All patients were febrile at enrolment. Caffeine (CYP1A2 substrate) pharmacokinetics was administered to assesses drug-metabolizing activity. The CYP1A2 activity was slightly lower in patients with malaria reflected by a 1.5-fold lower paraxanthine C_{max} and paraxanthine/caffeine ratio compared to healthy individuals. No differences were seen in caffeine C_{max} and $AUC_{0-\infty}$ (94). Similarly, 24 patients with visceral leishmaniasis were enrolled in a three-phase pharmacokinetic study, to establish the activity of CYP3A4, CYP2C19, and CYP2C9 before (phase 1), 2-5 days (phase 2) or 3-6 months (phase 3) after curative chemotherapy. Single dose midazolam (CYP3A4 substrate), omeprazole (CYP2C19 substrate), and losartan (CYP2C9 substrate) were administered at each time point. Midazolam clearance was 2-fold higher in phase 2, while no differences were seen in phase 3. Similarly, CYP2C19 activity increased following chemotherapy, with a 2-fold decrease in plasma omeprazole/5-hydroxyomeprazole ratio in phases 2 and 3 compared to baseline. CYP2C9 showed a trend towards increased activity following curative chemotherapy, however, due to large variations in urine losartan/E174 ratio in phase 1, the results were not statistically significant. The patients displayed elevated IL-6 concentrations (median 26.5 pg/ml) which decreased 6-fold in phase 2 and remained steady until phase 3 (95).

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4 Discussion

In this review, we have summarized the evidence linking inflammation to altered drug metabolism and drug transport **(Figure 1)**. Several studies in primary human hepatocytes have found that important inflammatory cytokines, such as IL-6 and IL-1β, downregulate CYP3A4 substantially, while other CYP enzymes are modestly downregulated. Clinical studies that examine the effects of inflammation on drug metabolism demonstrate considerable variability between studies and diseases. Overall, the clinical evidence suggests that CYP3A4 is moderately downregulated by acute and chronic inflammation, while other CYP enzymes are affected to a minor extent.

Several in vitro studies suggest that inflammatory cytokines strongly downregulate CYP enzymes and drug transporters to some extent (**Tables 1-3, S1, S3, and S4**). However, most of these studies have employed supraphysiological cytokine concentrations as high as 100- to 1000-fold above clinically relevant concentrations (**Table S1).** The concentration of cytokines required to induce half of the maximal downregulation (IC_{50}) of CYP enzymes in vitro is reached at much lower concentrations (**Table 2**). It is important to note that the IC_{50}-values of IL-1β and IL-6 for CYP enzymes (**Table 2**) correspond to concentrations of these cytokines observed in patients with different inflammatory diseases (Section 3.2.1 and 3.2.2). However, for other cytokines, such as TNF-α and IFN-γ, the dose-response curves are unknown. A few studies have investigated the impact of low concentrations of IL-6 on the enzyme activity of CYP3A4 (24,32,35,43,96) which resembles patient's physiology and CYP regulation more closely. Moreover, physiologically relevant cytokine combinations and concentrations could improve the understanding how systematic inflammation affects DMETs. A study explored the effect of combination of five cytokines, IL-6, IL-2, IL-10, TNF-α, and IFN-γ, at physiological relevant concentrations of 0.125 ng/ml and 2 ng/ml on the enzyme activity of CYP enzymes (96). These cytokine combinations decreased the enzyme activity of CYP3A4 and CYP1A2 by maximum of 2- and 4-fold, while CYP2D6, CYP2C9 and CYP2C19 were less affected. Although this is in line with the knowledge of these individual cytokines (**Tables 1, 2 and S3**), the downregulation of CYP1A2 may be potentiated in the presence of several cytokines.

Most in vitro studies investigated the effect of cytokines on the mRNA expression of CYP enzymes, but the strong downregulation of mRNA expression that is generally observed may not translate to in vivo. Several studies confirm the downregulation of CYP enzyme activity by

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cytokines (**Tables 1, 2 and S1**), but that the extent of dramatic downregulation of enzyme activity is modest compared to changes in mRNA, particularly for CYP3A4 (**Table 2 and S1**). However, measuring activity, in particular for transporters or enzymes without specific probes, is not always possible in vitro and thus protein concentrations may provide a suitable alternative. We identified only one study investigating the effect of cytokines on the protein expression of CYP enzymes in primary human hepatocytes (25). Moreover, downregulation of mRNA levels is rapid in primary human hepatocytes, while downregulation of protein levels and the subsequent enzyme activity is slower. Accordingly, the half-lives for downregulation of CYP3A4 mRNA and enzyme activity in micropatterned, long-term primary human hepatocyte cultures were 1.9 and 29 hours, respectively (26). In addition, the degradation-half lives of some CYP enzymes might be up to 100 hours (97). This implicates that several days of cytokine exposure on hepatocytes are needed before assessing the possible changes in the enzyme activity or protein amount of CYPs or transporters. Collectively, this highlights that cytokine-mediated downregulation of the mRNA levels of CYP enzymes or transporters should be interpreted with care and more knowledge is warranted regarding alterations in the most important endpoint that is the enzyme or transporter activity.

The main challenge for in vitro modelling of downregulation of CYP protein levels and enzyme activities is instability of the traditional 2D hepatocyte cultures during long-term culture (98). For example, a cross-laboratory study found up to 200-fold variation in IC_{50} values for IL-6-mediated suppression of CYP3A4 enzyme activity and mRNA expression in 2D hepatocyte culture, even when the same batch of hepatocytes was utilized (24). 2D primary hepatocyte cultures lose their DMET expression within a week, and thus if longer culture periods are warranted to study the effect of inflammatory cytokines on DMET activity and protein expression this culture format is not suitable. IL-6-mediated downregulation of CYP3A4 in a long-term culture of micropatterned hepatocytes was reproducible within five different hepatocyte donors indicating a robust response of this hepatocyte culture format during long-term studies (26). In addition to novel long-term primary human hepatocyte models, such as micropatterned hepatocytes and 3D hepatocytes (26,35,99,100), more advanced hepatic models containing non-parenchymal hepatic cells, such as Kupffer and endothelial cells, in static hepatic organoids, co-cultures or in microphysiological systems are potentially more physiological relevant models (35,99,101). Findings derived from novel cell models may improve translation of DMET modulation by inflammation.

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The concept of DDIs mediated by therapeutic proteins is rather new, although several well-designed studies on this topic are available (**Table 5**). Besides IL-6 antibodies and IL-6 receptor antibodies, none of the other current therapeutic proteins are linked to altered CYP metabolism. The IL-6 antibodies act as perpetrator, where the pharmacodynamics and derived alterations of IL-6 levels leads to changes in CYP activity and altered pharmacokinetics of the probe of interest. Hence, the DDI is not a direct pharmacokinetic interaction but rather a drug-disease-drug interaction. This emphasizes the need for DDI studies to be conducted in the relevant patient group with the relevant inflammatory level, for the results to be trustworthy and generalizable to the patients in which the drug should be used as treatment. In patients with rheumatoid arthritis, administration of a single dose IL-6 antibody or receptor antibody leads to approximately 2-fold upregulation of CYP2C19 and CYP3A4 (21,51,79), corresponding to the downregulation observed in patients with rheumatoid arthritis compared to healthy individuals (50,52). The regulation appears within one week and persists for at least 5 weeks after a single dose. Since steady state is not obtained until the second or third dose by these antibodies, single dose regimen may not fully reflect the extent of CYP modulation obtained in a clinical setting. Multiple dosing regimens is yet to be studied and may be valuable to fully understand this DDI and to provide meaningful recommendations on dose adjustments for co-medications.

Cytokine levels vary substantially between diseases and disease states. Additionally, different disease states might also result in various alterations of CYP enzymes. For example, studies in patients with rheumatoid arthritis (50) and Crohn's disease (60) showed that patients in remission had similar CYP activity as healthy individuals, while active disease state was associated with a decreased CYP activity (52,60). Considering the role of specific cytokines and not specific diseases, cytokine concentrations are likely to be stronger predictors of altered CYP activity. In clinical studies, cytokine concentrations are rarely measured (50,52,55,56,68,69,71,95), though it would increase our understanding on how inflammatory cytokines mediate the regulation of DMET. A few studies included the measurement of CRP (50,55). CRP is a rapid point-of-care test used in clinical practice as a quick paraclinical assessment of infection and inflammation. While convenient and widely available, current data do not support strong correlations between CRP and downregulation of drug metabolism in humans.

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The impact of inflammation on DMET regulation might be more important than ever due to the SARS-CoV-2 pandemic. A recent study among 170 hospitalized patients infected with SARS-CoV-2 evaluated the pharmacokinetics of lopinavir and hydroxychloroquine, both drugs which have been considered for the treatment of COVID-19 (102). The study found a downregulation of CYP3A4 correlated to CRP (102). While the results are valuable for this specific situation, they are hardly generalizable for other drugs, since multiple CYP enzymes metabolize lopinavir and hydroxychloroquine. While we recognize that pharmacokinetic studies are challenging to perform in specific patient groups, further studies assessing the impact of SARS-CoV-2 on drug metabolism is crucial to improve treatment of patients in the future.

4.1 Future perspectives

We have identified gaps in the current literature, which allows us to provide recommendations for future in vitro and clinical studies. We believe that advanced and long-term hepatic cell models, such as 3D primary human hepatocytes or microphysiological systems containing non-parenchymal hepatic cells, are ideal for assessing the impact of inflammation on DMETs. These models could allow robust assessment of extended exposures of cytokines and their effect on enzyme activity and protein expression of DMETs. When performing these studies, we encourage the use of clinically relevant concentrations and combinations of inflammatory cytokines to mimic physiological inflammation. Intestinal regulation of DMETs in inflammatory conditions is poorly understood. This is likely due to the lack of relevant human intestinal cell models. A clinical trial of patients with HIV, in which intestinal CYP3A4 (oral midazolam) was downregulated 2-fold while hepatic CYP3A4 (IV midazolam) was unaffected which highlights the need for understanding inflammatory regulation of intestinal DMET (72). This research area is expanding and primary small intestine cell models should allow assessment of inflammatory cytokines on intestinal first-pass metabolism and drug transport in future (103,104).

Currently, there is not sufficient evidence to provide clinical guidelines on how physicians should manage inflammation-mediated regulation of drug-metabolizing enzymes. Concomitant treatment should be closely monitored in case of acute infection or when initiating immune-modulating therapies, particularly for drugs with a narrow therapeutic interval. To increase our knowledge, we suggest that inflammation and cytokine concentrations are assessed routinely in future clinical

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studies to improve insight into the extent of inflammation. Such studies should be conducted in relevant patient populations to ensure baseline inflammation that may be affected by therapeutic proteins. The activity of the specific CYP enzyme should be assessed by specific probe drugs or pharmacokinetic cocktails to generate robust and generalizable results which can be applied to larger groups of drugs with similar metabolism. Whenever feasible, a self-controlled study design should be considered, to effectively reduce interindividual differences in physiology which could be expected in a non-disease control group. Finally, we recommend that multiple dosing is considered, especially for drugs with a long elimination half-life and slow onset of effect such as monoclonal antibodies.

In conclusion, the current literature provides clear evidence of inflammation and pro-inflammatory cytokines as factors that regulate expression and activity of drug-metabolizing enzymes and drug transporters in humans. We identified gaps between in vitro experiments and clinical data and find that in vitro studies are often conducted using supraphysiological cytokine concentrations far exceeding clinically relevant concentrations. Consequently, translation between in vitro findings and human clinical studies remains challenging. Despite this, we conclude that inflammation is associated with clinically relevant downregulation of CYP-enzymes, most importantly CYP3A4. The clinical impact of this is largely unknown and requires further evaluation. Interindividual variability in drug pharmacokinetics and response has been the subject for several decades of research. While inflammation alone will not explain all variability, it may be an important part of the puzzle and further understanding this may be significant for building models to support precision medicine.

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Figure Legends

FIGURE 1. Schematic illustration on how systemic inflammation decreases the activity of the drug metabolizing enzymes and transporters and the derived consequences on drug concentrations in acute disease and during immune-modulating treatment.

Table Legends

TABLE 1. Proinflammatory cytokines decrease the mRNA expression and enzyme activity of important drug-metabolizing cytochrome P450 (CYP) enzymes in primary human hepatocytes.[a]

TABLE 2. IL-6 and IL-1β downregulate the mRNA expression and/or activity of CYP enzymes in primary human hepatocytes in a concentration-dependent manner. The IC_{50} value describes the concentration resulting in half of the maximal downregulation.

TABLE 3. Proinflammatory cytokines decrease the expression of important hepatic uptake and efflux transporters in primary human hepatocytes.[a,b]

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TABLE 4. Inflammation in chronic and acute inflammatory diseases decrease the activity of CYP enzymes in an isoform-specific manner. Arrows indicate observed changes in CYP activity assessed by the specific probe drugs.*

TABLE 5. CYP enzyme activity is decreased in inflammatory diseases. Treatment with interleukin-6 antagonists and interleukin-6 receptor antagonists cause a normalization/increase of CYP enzyme activity. Arrows indicate observed changes in activity of the CYP enzyme, assessed by the specific probe drugs.*

Supplementary materials

1. Table S1
2. Table S2
3. Table S3 and S4
4. Table S5
5. Table S6

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TABLE 1. Proinflammatory cytokines decrease the mRNA expression and enzyme activity of important drug-metabolizing cytochrome P450 (CYP) enzymes in primary human hepatocytes.[a]

Cytokine	CYP3A4	CYP2D6	CYP2C9	CYP2C19	CYP1A2	CYP2C8	CYP2B6	Ref.
IL-6	↓↓↓ mRNA ↓↓↓ activity	↓ mRNA ↓ activity	↓↓ mRNA ↓ activity	↓↓ mRNA ↓↓ activity	↓↓ mRNA ↓↓ activity	↓↓ mRNA ↓↓ activity	↓↓ mRNA ↓-↓↓↓ activity	(24–42)
IL-1β	↓↓↓ mRNA ↓↓↓ activity	↓↓ mRNA	↓↓ mRNA	↓ mRNA	↓↓ mRNA ↓↓ activity	↓↓ mRNA	↔ mRNA	(25,28,35, 43,44)
TNF-α	↓↓↓ mRNA ↓↓ activity	↓ mRNA ↓ activity	↔ mRNA ↔ activity	↔ mRNA ↓↓↓ activity	↓ mRNA ↓↓ activity	↓↓ mRNA	↔ mRNA ↓ activity	(25,30,33)
IFN-γ	↓↓ mRNA		↓ mRNA	↔ mRNA		↓ mRNA	↓↓ mRNA	(25)

↓ = 1.25-2-fold, ↓↓ = 2-5-fold, ↓↓↓ = > 5-fold, ↔ = 0.81-1.24-fold

[a]A typical concentration of these cytokines applied to cells in vitro is 10 ng/ml.

Abbreviations: IL-6: Interleukin-6; IL-1β: Interleukin 1β; TNF-α: Tumor Necrosis Factor α; IFN-γ: Interferon-γ.

TABLE 2. IL-6 and IL-1β downregulate the mRNA expression and/or activity of CYP enzymes in primary human hepatocytes in a concentration-dependent manner. The IC_{50} value describes the concentration resulting in half of the maximal downregulation.

		IL-6		**IL-1β**	
Enzyme		IC_{50}	Maximum effect	IC_{50}	Maximum effect
CYP3A4	mRNA expression	3-454 pg/ml	↓13-100-fold	13-295 pg/ml	↓8-21-fold
	Enzyme activity	73-374 pg/ml	↓3-14-fold	22-416 pg/ml	↓3-50-fold
CYP2D6	mRNA expression	151 pg/ml	↓3-fold	945 pg/ml	↓4-fold
CYP2C9	mRNA expression	121 pg/ml	↓19-fold	229 pg/ml	↓5-fold
CYP2C19	mRNA expression	71 pg/ml	↓5-fold	153 pg/ml	↓2-fold
CYP1A2	mRNA expression	271-5490 pg/ml	↓5-6-fold	531 pg/ml	↓4-fold
	Enzyme activity	1251 pg/ml	↓4-fold	450 pg/ml	↓3-fold
CYP2C8	mRNA expression	153 pg/ml	↓26-fold	353 pg/ml	↓5-fold
CYP2B6	mRNA expression	70-177 pg/ml	↓4-32-fold		
References		(24,32,35,42)		(35,43,44)	

Abbreviations: IL-6: Interleukin-6; IL-1β: Interleukin 1β.

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TABLE 3. Proinflammatory cytokines decrease the expression of important hepatic uptake and efflux transporters in primary human hepatocytes.[a,b]

	P-gp (ABCB1)	**BCRP** (ABCG2)	**OCT1** (SLC22A1)	**MRP2** (ABCC2)	**OATP1B1** (SLCO1B1)	**OATP1B3** (SLCO1B3)	**OAT2** (SLC22A7)	Ref.
IL-6	↓ mRNA ↔ protein	↓ mRNA ↓ protein	↓↓↓ mRNA ↓ activity	↓ mRNA ↓ protein	↓↓↓ mRNA ↓ protein	↓↓ mRNA	↓ mRNA	(26,36,38,41,46,48)
IL-1β	↔ mRNA	↓↓ mRNA	↓↓↓ mRNA	↓ mRNA	↓↓↓ mRNA	↓↓↓ mRNA	↓↓ mRNA	(44,45,48)
TNF-α	↓ mRNA ↔ protein	↔ mRNA ↑ protein	↓↓↓ mRNA ↓ activity	↔ mRNA ↔ protein	↓↓ mRNA ↓ protein	↓↓ mRNA	↓↓↓ mRNA	(46,48)
IFN-γ	↓ mRNA	↓ mRNA	↔ mRNA	↓ mRNA	↓↓ mRNA	↓↓ mRNA	↔ mRNA	(47)

↓ = 1.25-2-fold, ↓↓ = 2-5-fold, ↓↓↓ = > 5-fold, ↔ = 0.81-1.24-fold

[a]Typical concentrations of these cytokines applied to cells in vitro are 1-100 ng/ml.

[b]The gene names of transporters are indicated inside brackets.

Abbreviations: IL-6: Interleukin-6; IL-1β: Interleukin 1β; TNF-α: Tumor Necrosis Factor α; IFN-γ: Interferon-γ; P-gp: P-glycoprotein; BCRP: Breast Cancer Resistance Protein; OCT1: organic cation transporter 1; MRP2: Multidrug Resistance-associated Protein 2, OATP: Organic Anion Transporting Polypeptide; OAT2: Organic Anion Transporter 2.

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TABLE 4. Inflammation in chronic and acute inflammatory diseases decrease the activity of CYP enzymes in an isoform-specific manner. Arrows indicate observed changes in CYP activity assessed by the specific probe drugs.*

	Impact on CYP activity (probe drugs)					
Disease (n)	**CYP3A4**	**CYP2D6**	**CYP2C9**	**CYP2C19**	**CYP1A2**	Ref.
Chronic inflammatory diseases						
Behcet's disease (52, 59)			↓ (Losartan[d])	↓↓ (Lansoprazole[d])		(57,58)
Cancer (10, 22)	↓ (Omeprazole[d])	↔ (Dextromethorphan[d])	↔ (Tolbutamide[a,b,c])	↔ (Omeprazole[d])	↔ (Caffeine[d])	(69,70)
Celiac disease (18)	↓ (Simvastatin[c])					(60)
Crohn's disease (14)	↓-↓↓↓ (Verapamil[a])					(59)
Diabetes (38)	↓ (Midazolam[d])	↔ (Dextromethorphan[d])	↔ (Tolbutamide[d])	↓ (Omeprazole[d])	↔ (Caffeine[d])	(66)
Hepatitis C (14, 35)	↓ (Midazolam[a,b])	↓↓↓ (Dextromethorphan[d])			↔ (Caffeine[d])	(74,75)
HIV (10, 30)	↓ (Midazolam[b])	↓-↓↓↓ (Dextromethorphan[a])			↔ (Caffeine[d])	(71,72)
Psoriasis (13)	↔ (Venlafaxine[a])	↔ (Venlafaxine[a])				(56)
Rheumatoid arthritis (8,12,14)	↔ -↓↓ (Verapamil[a])		↔ (Losartan[a])			(50,52,53)
Acute inflammatory diseases						
Parasitic diseases (10,24)	↓ (Midazolam[b])		↔ (Losartan[d])	↓ (Omeprazole[d])	↔ (Caffeine[a])	(94,95)
Sepsis (12)	↓↓↓ (Atorvastatin[a,c])					(90)
Surgery (10)					↔ (Theophylline[a,b])	(92)
Severe injuries (23)			↓ (Flurbiprofen[e])	↑↑ (Mephenytoin[e])		(93)

↓/↑ = 1.25-2-fold, ↓↓/↑↑ = 2-5-fold, ↓↓↓/↑↑↑ = > 5-fold, ↔ = 0.81-1.24-fold.

Empty cells indicate that the CYP-enzyme is not assessed by the reference. Only studies after year 2000 employing specific probe drugs are included.

*Pharmacokinetic parameter used to assess activity of the CYP enzyme: [a] Area under the concentration curve (AUC), [b] Clearance, [c] Maximum concentration (C_{max}), [d] Drug/metabolite ratio, [e] Urinary drug recovery.

Abbreviations: CYP: Cytochrome P450; HIV: Human Immunodeficiency Virus; n: number.

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TABLE 5. CYP enzyme activity is decreased in inflammatory diseases. Treatment with interleukin-6 antagonists and interleukin-6 receptor antagonists cause a normalization/increase of CYP enzyme activity. Arrows indicate observed changes in activity of the CYP enzyme, assessed by the specific probe drugs.*

Therapeutic protein	**Disease (n)**	**Impact on CYP activity (probe drugs)** CYP3A4	CYP2D6	CYP2C9	CYP2C19	CYP1A2	Ref.
IL-2R antagonist	Multiple sclerosis (20)	↔ (Midazolam[a])	↔ (Dextromethorphan[a])	↔ (Warfarin[a])	↔ (Omeprazole[a])	↔ (Caffeine[a])	(80)
IL-4R antagonist	Atopic dermatitis (14)	↔ (Midazolam[a])	↔ (Metoprolol[a])	↔ (Warfarin[a])	↔ (Omeprazole[a])	↔ (Caffeine[a])	(81)
IL-6 antagonist	Rheumatoid arthritis (12)	↑ (Midazolam[a])		↔ (Warfarin[a])	↑ (Omeprazole[a])	↓ (Caffeine[a])	(79)
IL-6R antagonist	Rheumatoid arthritis (19,12)	↑-↑↑ (Simvastatin[a])					(21,51)
IL-10	Healthy individuals (12)	↔ (Midazolam[b])	↔ (Dextromethorphan[d])	↔ (Tolbutamide[b])		↔ (Caffeine[b])	(89)
IL-17 antagonist	Psoriasis (24, 31)	↔ (Midazolam[a])					(82,83)
IL-23 antagonist	Psoriasis (21, 20, 14)	↔ (Midazolam[a])	↔ (Dextromethorphan[a]) ↔ (Metoprolol[a])	↔ (Warfarin[a])	↔ (Omeprazole[a])	↔ (Caffeine[a])	(84–86)
IFN-α	Hepatitis C (14, 26)	↔ (Midazolam[d])	↔ (Dextromethorphan[d])	↔ (Tolbutamide[d])		↔ (Caffeine[d])	(74,76)
	Healthy individuals (14)			↔ (Tolbutamide[a])	↔ (Mephenytoin[a])	↓ (Theophylline[a])	(77)
IFN-β	Multiple sclerosis (9)				↔ (Mephenytoin[d])		(78)
TNF-α antagonist	Healthy individuals (12)			↔ (Warfarin[a])			(87)

↓/↑ = 1.25-2-fold, ↓↓/↑↑ = 2-5-fold, ↓↓↓/↑↑↑ = > 5-fold, ↔ = 0.81-1.24-fold.

Empty cells indicate that the CYP-enzyme is not assessed by the reference. Only studies after year 2000 employing specific probe drugs are included.

* Pharmacokinetic parameter used to assess activity of the CYP enzyme: [a] Area under the concentration curve (AUC), [b] Clearance, [c] Maximum concentration (C_{max}), [d] Drug/metabolite ratio.

Abbreviations; IL: interleukin; INF: Interferon; n: number of subjects; R: receptor; TNF: tumor necrosis factor.

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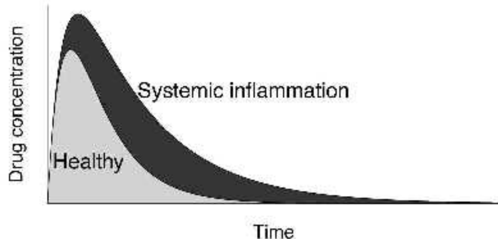
Systemic inflammation

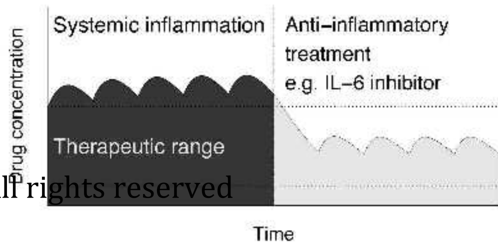
↑IL-6
↑IL-1β
↑IFN-γ
↑TNF-α

Healthy individuals

Intervention

↓ Activity of drug metabolizing enzymes
↓ Activity of drug transporters





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