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Review Article

The regulation of drug-metabolizing enzymes and membrane transporters by inflammation: Evidences in inflammatory diseases and age-related disorders

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ABSTRACT

Drug-metabolizing enzymes (DMEs) and membrane transporters play important roles in the absorption, distribution, metabolism, and excretion processes that determine the pharmacokinetics of drugs. Inflammation has been shown to regulate the expression and function of these drug-processing proteins. Given that inflammation is a common feature of many diseases, in this review, the general mechanisms for inflammation-mediated regulation of DMEs and transporters are described. Also, evidences regarding the aberrant expression of these drug-processing proteins in several inflammatory diseases and age-related disorders are provided.

1. Introduction

Pharmacokinetics describes the time course of drug levels in the body as a result of absorption, distribution, metabolism, and excretion (ADME) processes following administration. Absorption is a process in which the drugs transfer from the sites of administration to systemic blood circulation. Distribution is related to protein/tissue binding and the exchange of the drugs among various spaces in the body. Metabolism is the biotransformation process that generally converts the drugs to more water-soluble molecules, facilitating their excretion from the body. Excretion is the removal of drugs and/or their metabolites from the body, normally through the urinary or biliary pathways. It is known that drug-metabolizing enzymes (DMEs) and membrane transporters play important roles in the ADME processes.

The roles of DMEs in pharmacokinetics have been extensively investigated for years (for review, refer to Refs. [1,2]). The metabolism of drugs in the body can be mediated by enzymes responsible for phase I (oxidation, reduction, and hydrolysis) and/or phase II (conjugation) biotransformation.

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Among these, the cytochrome P450 (CYP) enzymes are well known for their roles in phase I oxidative metabolism; enzymes known for phase II metabolism include N-acetyl transferase, glutathione S-transferase (GST), uridine 5′-diphospho-glucuronosyltransferases (UGT), and sulfotransferase (SULT). On the other hand, membrane transporters are integral proteins that mediate the translocation of both endogenous and exogenous molecules across plasma or intracellular membranes. Transporters can be categorized into two superfamilies, namely ATP-binding cassette (ABC) transporters and solute carrier (SLC) transporters. The roles of transporters in drug absorption and disposition have been well characterized (for review, refer to Ref. [3]). Examples for the roles of DMEs and transporters involved in ADME processes are summarized in Table 1.

Under certain circumstances, the expression and activities of enzymes and transporters can be regulated, thereby leading to an alteration of the pharmacokinetic properties of substrate drugs. Intrinsic factors (e.g., disease, age, and gender) and extrinsic factors (e.g., drugs, smoking, alcohol use, and diet) can affect the pharmacokinetics of drugs, which may then result in insufficient efficacy or unwanted side effects. In recent years, disease–drug interaction is a rapidly growing field in drug discovery and has received much attention from drug development units and regulatory agencies. Given that inflammatory responses occurred in various diseases are known to be important for gene regulation, in this article, general mechanisms for inflammation-mediated regulation of DMEs and transporters are addressed. Also, examples regarding aberrant expression of these drug-processing proteins in inflammatory diseases (including type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease) and age-related disorders (including normal aging, metabolic disorders, and neurodegenerative diseases) are provided.

2. Factors contributing to gene regulation in inflammation

2.1. *The roles of cytokines in the regulation of DMEs and transporters*

Under inflammatory conditions, proinflammatory cytokines are not only produced locally around the pathological areas but may also be transferred through blood stream to activate inflammatory responses in distal tissues. In cultured human hepatocytes, direct treatments of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interferon-γ (IFN-γ), and transforming growth factor-β (TGF-β) can reduce the expression of CYP1A2, CYP2C8 and CYP3A4 [4,5]. Inhibition of IL-6 signaling using a specific antibody can abolish IL-6-induced inhibition of CYP1A2 and CYP3A4 activities in human hepatocytes [5]. Also, the knockout of IL-6 can attenuate the reduction of CYP enzymes (including Cyp1a2, Cyp2a5, Cyp2e1, and Cyp3a11) caused by turpentine treatment in mice [6]. Given that CYP enzymes and drug transporters share certain common regulatory pathways, the effects of cytokines on the regulation of CYP enzymes may be applicable to transporters. In mice, intraperitoneal administrations of TNF-α and IL-1β/IL-6 can reduce mRNA levels of Mrp2/Mrp3/Oatp2 and Mrp2/

Table 1 – Drug-metabolizing enzymes (DMEs) and transporters that are involved in ADME processes of pharmacokinetics.

Organs or tissues	Cell types	Subcellular localization	DMEs/transporters for drugs
Intestine	Intestinal epithelial cells (enterocytes)	Apical (luminal) membrane	OATPs, PEPT1, ASBT, MCT1, MDR1, BCRP, MRP2
		Inside the cell	Phase I DMEs: mainly CYPs
			Phase II DMEs: UGT, SULT, and GST
		Basolateral (abluminal) membrane	OCT1, OSTα/β, MRP1, MRP3
Liver	Hepatocytes	Basolateral (sinusoidal) membrane	OATPs, NTCP, OCT1, OAT2/7, OSTα/β, MRP3, MRP4, MRP6
		Inside the cell	Phase I DMEs: mainly CYPs
			Phase II DMEs: UGT, SULT, and GST
		Apical (canalicular) membrane	MDR1, BCRP, MRP2, BSEP, MATE1
Kidney	Renal tubular epithelial cells	Basolateral membrane	OCT2, OAT1-3, OATP4C1, OSTα/β, MRP3
		Apical membrane	OAT4, PEPT1/2, OCTN1/2, MDR1, BCRP, MRP2/4, MATE1, MATE2-K

ASBT: apical sodium dependent bile acid transporter; CYPs: cytochrome P450s; BCRP: breast cancer resistance protein; BSEP: bile salt export pump; DMEs: drug-metabolizing enzymes; GST: glutathione-S-transferase; MATE: multidrug and toxin extrusion protein; MCT: monocarboxylic acid transporter; MDR1: multidrug resistance protein 1 (P-glycoprotein; P-gp); MRP: multidrug resistance-associated protein; NTCP: sodium dependent cotransporting polypeptide; OAT: organic anion transporter; OATPs: organic anion transporting polypeptides; OCT: organic cation transporter; OSTα/β: heteromeric organic solute transporter; OCTN: organic cation/carnitine transporter; PEPT: peptide transporter; SULT: sulfotransferase; UGT: uridine 5′-diphosphate-glucuronosyltransferase.

Oatp1/Oatp2/Bsep, respectively [7]. The regulation of CYP enzymes and transporters by proinflammatory cytokines is summarized in Table 2. While the underlying mechanisms for the cytokine-induced gene regulation are not fully understood, it involves a number of transcriptional factors. Cytokines can alter the activities of various transcription factors, including nuclear factor-κB (NF-κB) and nuclear receptors. Details regarding the regulatory roles of NF-κB and nuclear receptors on DMEs and transporters are described in Sections 2.2 and 2.3, respectively.

2.2. *The roles of NF-κB in the regulation of DMEs and transporters*

NF-κB is a primary transcription factor that responds to diverse stimuli, including bacterial products and proinflammatory cytokines. NF-κB has been shown to regulate the gene expression of many hepatic CYP enzymes, including CYP2E1, CYP3A7, and CYP27B1 in humans, Cyp1a1, Cyp2b1/2, Cyp2c11, and Cyp2d5 in rats, and Cyp1a1 and Cyp3a11 in mice [8–10]. NF-κB is also shown to regulate the expression of numerous ABC and SLC transporters, including MDR1 in humans and Mdr1, Mrp2, Mrp3, Bcrp, Oatp1a4, Oatp2b1, and Ntcp in rats and mice [10–12].

2.3. *The roles of nuclear receptors in the regulation of DMEs and transporters*

Nuclear receptors are ligand-activated transcription factors. Typical nuclear receptors contain two common structural features, namely the N-terminal DNA-binding domain and the C-terminal ligand-binding domain. These two domains specifically recognize the targeted DNA sequences and ligands, respectively. Based on their dimerization and DNA binding properties, nuclear receptors can be categorized into four groups (for review, refer to Ref. [13]). Class I nuclear receptors include steroid hormone receptors, such as glucocorticoid receptor (GR) and progesterone receptor (PR); class II include pregnane X receptor (PXR), constitutive androstane receptor (CAR), liver X receptor (LXR), peroxisome proliferator-activated receptors (PPARs) and farnesoid X receptor (FXR); class III include hepatic nuclear factors (HNFs), germ cell nuclear factor I (GCNF) and retinoid X receptors (RXRs); class IV include estrogen receptor-related receptor-α (ERR) and nuclear receptor 5A1 (SF-1). Class I and II nuclear receptors have been extensively investigated, while studies regarding class III and IV nuclear receptors are relatively limited.

Among nuclear receptors, class II nuclear receptors, especially PXR and CAR, are probably most noteworthy because many of them are considered as xenobiotic sensors. PXR is highly expressed in the liver and intestine and is considered to regulate genes whose encoded proteins protect the body against xenobiotics. Many drugs such as dexamethasone, mifepristone (RU486) and rifampicin are activators of PXR [14]. The transcriptional activity of PXR is also dependent on various endogenous steroids including progesterone and its metabolites [15]. The most notable target gene activated by PXR may be *CYP3A4*, in which CYP3A4 protein metabolizes more than 50% of the clinical therapeutic agents [16]. PXR also mediates the expression of other phase I DMEs (e.g., CYP2B6 [17]; and CYP2Cs; [18–20]) and phase II DMEs (e.g., GST, UGT, and SULT [21]) in humans. In addition to its effect on enzymes, the expression of mouse hepatic basolateral Oatp2 and canalicular Mrp2 has been shown to be upregulated in response to the treatment of PXR ligands [22,23]. In the intestinal epithelial cells and brain microvascular endothelial cells, PXR was reported to upregulate the expression of Mdr1 at the luminal membrane to limit the absorption and distribution of molecules into the enterocytes and the brain, respectively [24,25]. In terms of CAR, it was originally explored

Table 2 – The regulation of CYP enzymes and transporters by lipopolysaccharide (LPS) treatment and proinflammatory cytokines.

Inflammatory stimulus and cytokines	Species	Target	References
LPS	Human	Decreased expression of CYP2C8 and CYP3A4	[4]
	Rat	Decreased expression of Cyp3a1, Cyp3a2, Mrp2, Mrp6, Mdr1a, Oatp1, Oatp2, Ntcp, Bsep, Oct1, and Oct3	[49,50]
	Mouse	Decreased expression of Cyp1a2, Cyp2a5, Cyp2c29, Cyp2e1, Cyp3a11, Cyp4a10, and Cyp4a14 Increased expression of Cyp3a13	[51]
TNF-α	Human	Decreased expression of CYP2C8 and CYP3A4	[4]
	Mouse	Decreased expression of Mrp2, Mrp3, and Oatp2	[7]
IL-1β	Human	Decreased expression of CYP2C8 and CYP3A4	[4]
	Mouse	Decreased expression of Mrp2, Oatp1, Oatp2, and Bsep	[7]
IL-6	Human	Decreased expression of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4	[4,5]
	Mouse	Decreased expression of Cyp1a2, Cyp2a5, Cyp2e1, Cyp3a11, Mrp2, Oatp1, Oatp2, and Bsep	[6,7]
IFN-γ	Human	Decreased expression of CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4	[4]
TGF-β	Human	Decreased expression of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4	[4]

Bsep: bile salt export pump; CYP: cytochrome P450; IFN-γ: interferon-γ; IL-1β: interleukin-1β; IL-6: interleukin-6, LPS: lipopolysaccharide; Mdr1: multidrug resistance protein 1 (P-glycoprotein; P-gp); Mrp: multidrug resistance-associated protein; Ntcp: sodium dependent cotransporting polypeptide; Oatp: organic anion transporting polypeptide; Oct: organic cation transporter; TGF-β: transforming growth factor-β; TNF-α: tumor necrosis factor-α.

for the induction of CYP2B genes in response to phenobarbital treatment [26] and was later demonstrated to have a role in the regulation of a wide range of genes involved in phase I and phase II metabolism [21]. The activation of CAR has also been reported to induce phase III drug elimination pathways (i.e., transporter-mediated clearance), including MDR1 in humans [27] and Oatp2 and Mrp2 in rats [28,29]. CAR is primarily expressed in the liver with lower levels in the heart, kidney, brain, and lung [30]. PXR and CAR overlap in many aspects (e.g., ligands, action mechanisms, and target genes) and both are important regulatory factors for gene expression of enzymes/transporters [31].

Although PPARα, LXR, and FXR also belong to class II nuclear receptors, they are known for their roles in lipid metabolism [32]. Nevertheless, these nuclear receptors also contribute to the gene transcription of CYP2B6, CYP2C29, CYP3A4, CYP3A11, and MRP2 in humans [29,33–35] and Oatps and Mrp2 in rodents [34,36,37]. As for class I nuclear receptors, GR can increase gene transcription of various DMEs either by direct binding to the promoter of target genes (e.g., *CYP3A5*, *CYP2C9*, and *CYP2C19*) or through the interaction with other nuclear receptors (e.g., HNF-4α and PXR) to induce gene transcription (e.g., *CYP2A6*, *CYP2B6* and *CYP3A4*) in humans [38–41]. For class III nuclear receptors, HNF-1α and HNF-4α are critical for regulating gene expression in the liver and kidney [42–46]. It is also noted that HNF-4α activates CYP3A4 expression not only through direct binding to *CYP3A4* promoter but also through PXR- and CAR-mediated pathways [47]. These findings suggest that the interplay among nuclear receptors shapes the regulation of drug-processing proteins and thereby potentially affects the ADME profiles of their substrate drugs. The regulation of CYP enzymes and transporters via NF-κB and nuclear receptors is summarized in Table 3.

3. Aberrant expression of DMEs and transporters in inflammatory diseases and age-related disorders

While the influence of inflammation on the expression of enzymes/transporters is an important issue, most of the published articles focused on inflammation models induced by lipopolysaccharide (LPS) treatment or bacterial/viral/parasitic infection (for review, refer to Ref. [48]). LPS treatment increases the levels of proinflammatory cytokines along with decreased expression of numerous DMEs and transporters [49–51] (Table 2), showing that bacterial component-induced inflammation is notable for its impacts on pharmacokinetics of drug. This LPS-mediated gene regulation is also associated with the changes in the expression and activity of nuclear receptors and transcription factors [52,53].

In addition to LPS-induced inflammation, inflammation is involved in the pathogenesis of many diseases, including inflammatory diseases (e.g., type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease) and age-related disorders (e.g., normal aging, metabolic disorders, and neurodegenerative diseases) [54,55]. Compared to LPS-induced

Table 3 – The regulation of CYP enzymes and transporters by ligand-activated nuclear receptors and NF-κB.

Nuclear receptors/transcription factors	Species	Target	References
PXR	Human	CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, MDR1, MRP2	[16–20,24,29]
	Rat	Mrp2	[23]
	Mouse	Cyp3a11, Bsep, Mdr1a, Mrp2, Mrp3, Oatp2	[22,25]
CAR	Human	CYP2C19, CYP3A4, MDR1	[18,27]
	Rat	Cyp3a23, Mrp2, Oatp2, Bsep	[28,29]
	Mouse	Cyp2b10	[26]
GR	Human	CYP2A6, CYP3A4, CYP3A5, CYP2B6, CYP2C8, CYP2C9, CYP2C19, MDR1	[38–41]
HNF-1α	Human	CYP1A2	[42]
	Rat	Cyp2e1	[43]
HNF-4α	Human	CYP2A6, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2D6, MDR1, ABCB11, MRP2, OATP1B1, OCT1	[40,44–47]
PPARα	Human	CYP3A4	[35]
	Mouse	Cyp2a1, Cyp2a4, Cyp2a5, Cyp2c29, Cyp3a11	[37]
LXR	Human	CYP3A4, CYP2B6, MRP1, MRP2	[33,34]
	Rat	Mrp1, Mrp2	[34]
FXR	Human	MRP2	[29]
	Rat	Mrp2	[29]
	Mouse	Oat3, Oatps, Oct2, Octn1	[36]
NF-κB	Human	CYP1A1, CYP2B1/2, CYP2C11, CYP2C11, CYP2D5, CYP2E1, CYP3A7, CYP27B1, MDR1	[9,12]
	Rat	Cyp1a1, Cyp2b1/2, Cyp2c11, Cyp2d5, Mdr1	[9,11]
	Mouse	Cyp1a1, Cyp3a11, Mdr1a, Mrp2, Mrp3, Abcb11, Bcrp, Oatp1a4, Oatp2b1, Ntcp	[8–10]

ABCB: ATP-binding cassette transporter B; Bcrp: breast cancer resistance protein; Bsep: bile salt export pump; CAR: constitutive androstane receptor; CYP (Cyp): cytochrome P450; GR: glucocorticoid receptor; HNF: hepatocyte nuclear factor; MDR1 (Mdr1): multidrug resistance protein 1 (P-glycoprotein; P-gp); MRP (Mrp): multidrug resistance-associated protein; NF-κB: nuclear factor-κB; Ntcp: sodium dependent cotransporting polypeptide; Oat: organic anion transporter; OATP (Oatp): organic anion transporting polypeptide; OCT (Oct): organic cation transporter; Octn: organic cation/carnitine transporter; PPAR: peroxisome proliferator-activated receptor; PXR: pregnane X receptor.

models, inflammatory human diseases are more complex and their impacts on the expression and activity of enzymes/transporters should be evaluated individually. As summarized in Table 4, in this article, the regulation of DMEs and transporters is reviewed for type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease. In addition, as aging is recognized as a universal and multisystemic disease [56] and age-related disorders are characterized by different degrees of inflammation, the regulation of enzymes/transporters is also reviewed in normal aging, metabolic disorders (e.g., type 2 diabetes and obesity), and neurodegenerative diseases.

3.1. *Type 1 diabetes*

Type 1 diabetes (T1D) is an autoimmune disease with selective death of β-cells. Insulin therapy is the preferred treatment for T1D management. During the disease progression, aberrant inflammatory signalings (including cytokines and NF-κB activation) are associated with the development of multiple complications (e.g., cardiovascular, retinal, and renal complications) in T1D [57]. In the liver biopsies of patients with T1D, both total CYP content and the metabolizing capacity (using antipyrine as a probe drug for the activities of CYP1A2, CYP2C, and CYP3A) were reported to be increased, compared with those of non-diabetic subjects [58,59]. Also, the pharmacokinetic properties of various drugs are changed in patients with T1D. For example, higher oral clearance of theophylline (mainly metabolized by CYP1A2, CYP2E1, and CYP3A4 in humans) and lower steady-state plasma concentrations of phenytoin (mainly metabolized by CYP2C9 in humans) were shown in T1D patients. In contrast, a reduced clearance of lidocaine (mainly metabolized by CYP3A in humans) was reported in T1D patients (review by Refs. [59,60]). Likewise, the expression of many CYP enzymes has been demonstrated to be altered in T1D animal models [60]. In rats and mice with streptozotocin (STZ)-induced T1D, hepatic expression of numerous CYP isozymes (Cyp1a2, Cyp1b1, Cyp2b1, and Cyp2e1 in rats; Cyp1a1, Cyp2b9, Cyp2b10, Cyp3a11, Cyp4a10, and Cyp4a14 in mice) are increased [61,62]. Corroboratively, higher systemic exposure of monoethylglycinexylidide, the metabolite of lidocaine (converted by Cyp1a2 and Cyp3a2), was observed in STZ-treated rats receiving single intravenous administration of lidocaine [63]. Also, higher clearance of fluorouracil (metabolized by Cyp1a1/2) was reported in STZ-induced T1D rats [64]; apparent total clearance of triazolam (metabolized by Cyp3a11) was increased in STZ-treated mice than in controls [65]. The induction of CYP enzymes in STZ models may be related to NF-κB activation in the liver [66]. In addition to CYP enzymes, drug transporters are also regulated in T1D. For examples, hepatic expression of Mdr2 and renal expression of Mdr1 are significantly increased, whereas intestinal expression of Mdr1 is decreased in STZ-induced T1D rats [67–69]. On the other hand, the regulation of Mdr1 expression at the blood–brain barrier remains controversial in STZ-treated rats [70,71]. Despite that the expression of CYP enzymes and transporters are changed in T1D, pharmacokinetic data obtained from T1D animal models are not quite consistent with those from human T1D patients [60]. Thus, extrapolating data from T1D animals to humans needs to be careful.

3.2. *Rheumatoid arthritis*

Rheumatoid arthritis (RA) is an autoimmune disease characterized by severe systemic inflammation. The production of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6, are elevated in blood circulation and synovial fluid throughout the disease stages [55]. Adjuvant- and collagen-induced arthritis rat models are widely used to mimic human RA. Studies conducted using these animal models have demonstrated that chronic inflammation in RA is not only crucial for disease progression but also influential on drug pharmacokinetics. Pharmacokinetic studies have shown that the plasma concentrations of verapamil and propranolol are significantly increased, due to the decreased clearance, in rats with adjuvant-induced arthritis [72,73]. This was suggested to be mediated by the downregulation of hepatic Cyp2b1, Cyp2b2, Cyp3a1, and Cyp3a2 in RA [73,74]. Likewise, in collagen-induced arthritis (CIA) rats, the mRNA levels of intestinal *Cyp3a1* and hepatic *Cyp2c6/7* and *Cyp3a1* are markedly decreased, leading to differential changes in the pharmacokinetics of statins [75]. The expression changes in Cyp2b and Cyp3a enzymes are strongly correlated with the increased levels of TNF-α, IL-1β, and IL-6 in the liver [74]. Inhibition of cytokines production by non-steroidal anti-inflammatory drugs (NSAIDs) or treatment with antibodies against specific cytokines can reverse the reduction of CYP enzymes and the changes in the clearance of propranolol in RA animal models [76,77], confirming that cytokines have an important role in the regulation of CYP enzymes in RA. In humans, it was recently reported that the levels of inflammatory cytokines are negatively associated with CYP3A4 phenotype in RA patients [78]. On the other hand, in terms of membrane transporters, the mRNA levels of numerous ABC and SLC transporters (e.g., *Oatps*, *Mdr1a*, *Mrp2*) are decreased in adjuvant- or collagen-induced arthritis rats [75,79]. The downregulation of *Oatp1a1*, *Oatp1b2* and *Oatp1a4* can reduce hepatic uptake of fluvastatin and atorvastatin in CIA rats [75]. These changes in transporter expression in RA are considered to be mediated by the cytokine-induced downregulation of PXR, but not of CAR [79].

3.3. *Inflammatory bowel disease*

Inflammatory bowel disease (IBD) is a type of disorder that is characterized by chronic and progressive inflammation in the intestine and colon. Ulcerative colitis (UC) and Crohn's disease (CD) are two common forms of IBD. A study using DNA microarray showed a broad downregulation of genes involved in drug metabolism in the colon biopsy specimens obtained from both UC and CD patients. The expression of MDR1, but not of MRP2/3, is significantly decreased in colon samples of UC patients. This dysregulation is accompanied by a severe reduction of PXR expression [80]. To investigate the regulation of enzymes/transporters in IBD and the underlying mechanisms, several studies have been conducted using both infectious and chemical-induced animal models of IBD. Similar to the findings observed in human IBD, the gene and protein expression of many CYP enzymes are generally downregulated in the liver of these IBD animals. The changes in CYP enzymes are in parallel with increased levels of cytokines [81–83],

Table 4 – The regulation of CYP enzymes and transporters in animal models of human inflammatory diseases.

Diseases	Models	Organs or tissues	Drug-processing proteins
Type 1 diabetes	Streptozotocin-induced diabetic rat model	Liver	Increased expression of Cyp1a2, Cyp1b1, Cyp2b1, Cyp2e1, and Mdr2 [61,67]
		Intestine	Decreased expression of Mdr1 [68]
		Kidney	Increased expression of Mdr1 [69]
		Blood–brain barrier	Increased or decreased expression of Mdr1 [70,71]
	Streptozotocin-induced diabetic mouse model	Liver	Increased expression of Cyp1a1, Cyp2b9, Cyp3a11, Cyp4a10, Cyp4a11, and Mdr2 [62]
Rheumatoid arthritis	Adjuvant-induced arthritis rat model	Liver	Decreased expression of Cyp 1a1/2, Cyp2b1, Cyp2b2, Cyp3a1, Cyp3a2, Mdr1a, Mrp2, Oatp1a1, Oatp1a4, Oatp1a5, Oatp1b2, and Oatp2b1 [73,74,79]
		Intestine	Decreased expression of Mrp2, Bcrp, Lat2, and Oatp1a5 [79]
	Collagen-induced arthritis rat model	Liver	Decreased expression of Cyp2c6, Cyp2c7, and Cyp3a1 [75]
		Intestine	Decreased expression of Cyp3a1, Oatp1a1, Oatp1a4, Oatp1b2, and Mrp2 [75]
Inflammatory bowel disease	Trinitrobenzene sulfonic acid-induced colitis rat model	Liver	Decreased expression of Cyp1a2, Cyp2c11, Cyp2e1, and Cyp3a2 [82]
	Dextran sulfate sodium-induced colitis mouse model	Liver	Decreased expression of Cyp1a2, Cyp2a5, Cyp2b9, Cyp2c29, Cyp2d9, Cyp3a25, Cyp4a10, and Cyp4a14 Increased expression of Cyp3a11, and Cyp3a13 [83]
Aging	Normal aging rats	Liver	Decreased expression of Cyp1a1, Cyp1a2, Cyp2b1, Cyp2c11, Cyp2e1, and Cyp3a2 [92]
	Normal aging mice	Liver	Decreased expression of Cyp1a2, Cyp2b10, Cyp3a11, Oatp1a1, Ent1, and Mrp6 Increased expression of Oat2, Oatp1a4, and Mrp4 [93,94]
Metabolic disorders and type 2 diabetes	High fat diet and streptozotocin-induced type 2 diabetic rat model	Liver	Decreased expression of Mrp5 [104]
		Kidney	Decreased expression of Oct2 Increased expression of Mrp2, Mrp4, Bcrp, and Oat2 [104]
	High fat diet-fed rats	Liver	Decreased expression of Cyp3a and Mdr1 [98]
	High fat diet-fed mice	Liver	Decreased expression of Cyp2a4, Cyp2b10, and Cyp3a11 [97]
	ob/ob mice	Liver	Decreased expression of Oatp1a1 and Ntcp [103] Increased expression of Cyp2a, Cyp2b, Mrp2, and Mrp4 [99,100]
		Kidney	Decreased expression of Mrp3, Oatp1a1, and Oat2 [103]
	db/db mice	Liver	Decreased expression of Cyp1a2 Increased expression of Cyp2b and Cyp4a [101]
	TSOD mice	Liver	Decreased expression of Cyp1a and Cyp2e Increased expression of Cyp2c and Cyp3a [102]
	Monosodium glutamate-induced obese mouse model	Intestinal duodenum	Decreased expression of Mdr1 [106]
		Intestinal jejunum	Increased expression of Mdr1 [106]
	NZO mice	Renal tubule	Decreased expression of Mdr1 [107]
		Blood–brain barrier	Increased expression of Mdr1 [105]
Alzheimer's disease	Tg2576 mice	Blood–brain barrier	Decreased expression of Mdr1 [112]
Huntington's disease	R6/2 mice	Blood–brain barrier	Increased expression of Mdr1 [113]
Epilepsy	Pilocarpine-induced acute and chronic epileptic rat model	Blood–brain barrier	Increased expression of Mdr1 [114]

Bcrp: breast cancer resistance protein; Cyp: cytochrome P450; Ent1: equilibrative nucleoside transporter 1; Lat2: L-type amino acid transporter 2; Mdr1: multidrug resistance protein 1 (P-glycoprotein; P-gp); Mdr2: multidrug resistance protein 2; Mrp: multidrug resistance-associated protein; Ntcp: sodium dependent cotransporting polypeptide; NZO: New Zealand obese; Oat: organic anion transporter; Oatp: organic anion transporting polypeptide; Oct: organic cation transporter; TSOD: Tsumura, Suzuki, obese, diabetes.

suggesting inflammation in the colon can affect hepatic drug metabolism. Treatments of anti-inflammatory agents and antibiotics are both sufficient to attenuate the downregulation of hepatic CYP enzymes in IBD models [81–83], suggesting that the disturbance of CYP enzymes in IBD is, at least in part, caused by the combination effect of colonic inflammation and bacteria-derived molecules (e.g., endotoxin or LPS). Given that PXR expression is almost absent in colonic samples from human with IBD [80], the role of PXR dysregulation in inflammatory signaling of IBD has been extensively investigated. PXR activation has been proposed as a novel target for IBD therapy [84]. Nevertheless, the expression and activity of PXR in hepatic and renal samples from either human IBD or animal IBD model need to be further evaluated.

3.4. *Aging*

Human aging has been described as a chronic and low-grade inflammatory condition [85]. Under this condition, NF-κB and nuclear receptor signalings are found to be regulated during aging [86,87]. As described above, the transcription factors contribute to the regulation of enzymes/transporters, suggesting that aging can be a regulatory factor for drug metabolism/transport. However, the effects of aging on the expression and activity of CYP enzymes are controversial. The expression of many, but not all, CYP enzymes (e.g., CYP1A2, CYP2C9, CYP2C10, CYP2C18. and CYP2C19) was shown to be reduced in human aging population (reviewed by Ref. [88]). Using in-vivo metabolic probes (cocktail substrates for CYP1A2, CYP2C19, CYP2D6, CYP2E1, and CYP3A4), the metabolic activities of CYP2C19, CYP2E1, and CYP3A4, but not of CYP1A2 and CYP2D6, seem to be dependent on age [89]. However, the regulation of CYP3A4 expression during aging remains controversial [90,91] and the conditions may vary among aged human individuals due to their personal medical history. In this regard, using normal aging animals may be a promising strategy to clarify the impact of aging on the expression of enzymes/transporters [92,93]. In a study that analyzed mRNA expression of hundreds of detoxification enzymes in aged mice, the results showed that about 40–45% of these genes were downregulated during aging process [94]. Still, age-related disorders that are commonly developed during aging, rather than aging itself, may also dominate gene regulation in these animal models.

3.5. *Metabolic disorders*

Aging is a critical risk factor for the development of metabolic disorders. It is generally believed that chronic inflammation during aging is the major cause of metabolic abnormalities (including hyperglycemia, hyperlipidemia, insulin resistance, and obesity) that are characterized in type 2 diabetes (T2D). Total CYP content in liver biopsies of patients with T2D was reported to be decreased [58]. Consistently, patients with T2D were found to have lower CYP3A4 activity [95]. In contrast, the activity of CYP2E1 was increased and the activities of CYP1A1, CYP2C9 and CYP3As remain unchanged in patients with T2D [59,96]. In animal models with metabolic disorders, the mRNA levels of *Cyp3a11*, *Cyp2b10*, and *Cyp2a4* have been demonstrated to be significantly reduced in the liver of high-fat diet-fed mice when compared with those in low-fat diet-fed mice [97]. Downregulation of hepatic Cyp3a and Mdr1 was shown to be related to the increased plasma levels of nelfinavir in high-fat diet-fed rats after an intravenous injection [98]. In addition to diet-manipulated mouse models, the regulation of DMEs has been examined in genetic diabetic mouse models. The *ob/ob* mice, which carry a mutation in the gene responsible for the production of leptin, can develop obesity and mild hyperglycemia similar to many cases of human T2D. In this mouse model, total levels of CYP enzymes are significantly lower, compared with lean mice. Yet, while Cyp2e1 activity is lower, the activities of Cyp2a and Cyp2b are higher in *ob/ob* mice than in controls. Leptin administration can correct the alterations, suggesting that the regulation of CYP enzymes may be due to direct effects of leptin or via indirect changes in insulin or endogenous hormones [99,100]. On the other hand, in *db/db* mice, another spontaneous obesity-induced diabetic mouse model carrying a mutation gene for leptin receptor, protein levels of Cyp2b and Cyp4a enzymes are increased, while that of Cyp1a2 is decreased. The protein levels of Cyp2c, Cyp2e1, and Cyp3a are not different between *db/db* and wild-type mice [101]. In TSOD (Tsumura, Suzuki, obese, diabetes) mice, higher levels of Cyp2c and Cyp3a, but lower levels of Cyp1a and Cyp2e enzymes have been reported. Following an intraperitoneal injection of triazolam, a substrate for Cyp3a, its clearance was significantly higher in TSOD mice than in controls [102]. Overall, these findings suggest that the regulation of CYP enzymes in T2D may depend on the disease models and CYP isoforms.

The expression of drug transporters is also altered in obesity and T2D [103–107]. In the liver of *ob/ob* mice, the expression levels of several uptake transporters (e.g., Oatps and Ntcp) are decreased, whereas the levels of efflux transporters such as Mrp2 and Mrp4 are increased [103]. In the kidney of *ob/ob* mice, the expression of Mrp3, Oatp1a1, and Oat2 is decreased [103]. In a polygenic T2D mouse model, New Zealand obese mice, the protein expression of Mdr1 is significantly increased in the brain and the blood–brain barrier [105], but decreased in renal tubules [107].

In addition to inflammation, several other mechanisms have been proposed to account for the regulation of enzymes/transporters in the models of metabolic disorders described above. Higher serum levels of glucose and insulin are observed in early stage of T2D. Therefore, hyperglycemia and hyperinsulinemia are considered to induce the changes in the expression of enzymes/transporters in T2D. This idea has been further confirmed by both in-vitro and in-vivo experiments [105,108,109]. Although it remains unclear how glucose and insulin influence gene transcription, it is noted that the expression of several transcription factors, including CAR, RXRα, PXR, HNF-4α, and NF-κB, is also modulated in these models [101,102,105].

3.6. *Neurodegenerative diseases*

Neurodegenerative diseases are a group of chronic brain disorders that are characterized by a progressive loss of neurons. While diverse neurodegenerative diseases are identified in humans, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS), neuroinflammation is a common characteristic of these

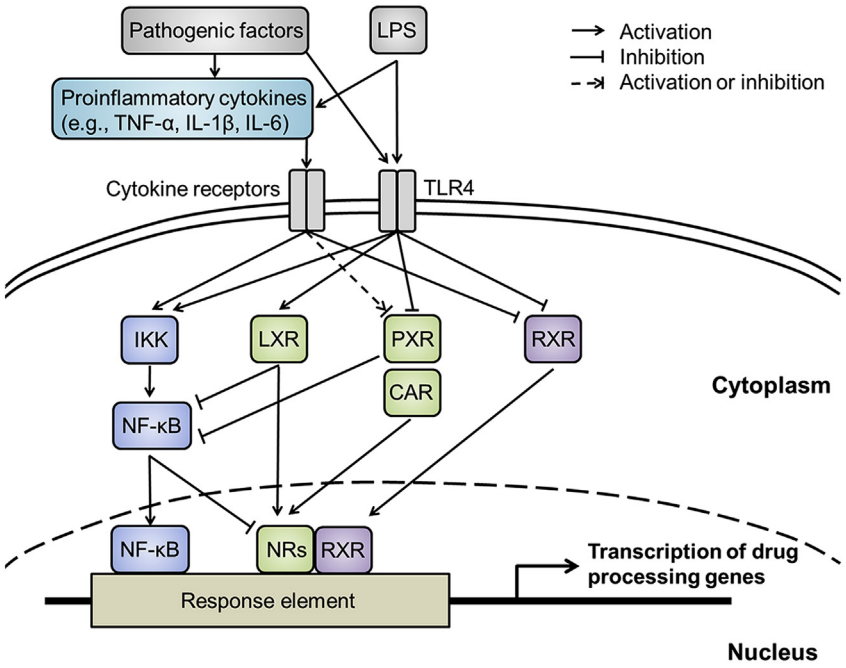

Fig. 1 – The illustration of inflammation-mediated gene regulation through NF-κB and nuclear receptor pathways under disease conditions. CAR: constitutive androstane receptor; IKK: IκB kinase; IL-1β: interleukin-1β; IL-6: interleukin-6; LPS: lipopolysaccharide; LXR: liver X receptor; NF-κB: nuclear factor-κB; NRs: nuclear receptors; PXR: pregnane X receptor; RXR: retinoid X receptor; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor-α.

diseases (for review, refer to Refs. [54,55]). Neuroinflammation describes the activation of glial cells, especially microglia and astrocytes within the brain, which release a wide range of proinflammatory cytokines and chemokines that cause neurotoxicity. Although neuroinflammation is a hallmark for neurodegenerative diseases, little is known for the impacts of neuroinflammation on the expression of enzymes/transporters or on the pharmacokinetics of administered drugs. Instead, current findings in literature mainly focus on the roles of enzymes/transporters in the development of neurodegenerative diseases. For examples, the expression and function of CYP2D6 are involved in the formation of neurotoxin that induces parkinsonism [110]; reduced function of Mdr1 at the blood–brain barrier in AD and PD-related disorders may impair brain clearance of β-amyloid [111,112]. Until recently, a study demonstrated that the mRNA and protein expression levels of Mdr1 at the blood–brain barrier are increased in R6/2 HD mouse model through NF-κB pathway, which then affects brain availability of antipsychotic drugs risperidone and paliperidone [113]. Likewise, the protein expression and activity of Mdr1 are increased in brain capillaries in pilocarpine-induced acute and chronic epileptic rats [114]. These observations suggest that the regulation of drug-processing proteins in either neurodegenerative or neurological diseases is worth an attention.

4. Conclusions and future directions

Accumulating evidences have demonstrated that the expression of DMEs and transporters can be regulated under inflammation (Fig. 1). In agreement with this notion, aberrant expression of these drug-processing proteins is observed in several animal models of human inflammatory diseases. The examples include, but are not limited to, type 1 diabetes, rheumatoid arthritis, inflammatory bowel disease, normal aging, metabolic disorders, and several neurodegenerative diseases. Thus, following the same drug administrations, patients with these diseases may be subject to different pharmacokinetic profiles from those without the same disease states. Although experimental animal models of human diseases seem to offer a feasible opportunity to explore this issue, the gap between experimental disease models and clinical observations needs to be considered. Unraveling the underlying molecular mechanisms of these regulations can enable us to see the whole picture and provide better prediction for the therapeutic outcome.

Conflicts of interest

The authors declare no conflicts of interest.

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