(Kreb 2006, Michalski et al. 2002). Taking such information into account, the failure of hepatic excretion of troglitazone sulfate might lead to hepatotoxicity, although troglitazone sulfate itself is pharmacologically inactive and did not exhibit cytotoxicity in human hepatoma cells (Loi et al. 1999; Yamamoto et al. 2001)

Using knockout rats lacking multidrug resistant associated protein-2 (Mrp2), it has been demonstrated that troglitazone glucuronide is a substrate for Mrp2 (Kostrubsky et al. 2001). Therefore, the troglitazone glucuronide formed in enterocytes might be excreted to the intestinal lumen via transporters such as Mrp2 expressed in the brush border membrane. Then, the glucuronide would again be converted to troglitazone by β-glucuronidase and the troglitazone might be reabsorbed. There has been no reported evidence that M2 is responsible for the hepatotoxic effects of troglitazone.

6 Hypersensitivity Reaction Associated with Troglitazone Hepatotoxicity

Idiosyncratic adverse reactions are difficult to study because of their rare occurrence, dose-independence, and lack of reproducibility in experimental animal models. Many idiosyncratic drug reactions have an immunological (hypersensitivity) basis, whereas some are due to a metabolic abnormality of the host (Pohl et al. 1988; Ju and Uetrecht 2002). Idiosyncratic drug-induced hepatitis has been assumed to be mediated by immunogens formed by covalent interaction of a reactive drug metabolite with cellular macromolecules (Park et al. 1998). The bioactivated immunogens may not only lead to an immune response directed against the haptenic epitope and the neoantigen, but also against autoantigenic determinants, which is characterized by the formation of autoantibodies (Pohl et al. 1988). A number of hepatotoxic drugs have been reported to produce autoantibodies. For example, antiprotein disulfide isomerase, antimicrosomal carboxyesterase, anticalreticulin, anti-ERp72, anti-GRP78, anti-GRP94, and anti-CYP2E1in halothane hepatitis (Bourdi et al. 1996; Gut et al. 1993; Kenna et al. 1993; Pumford et al. 1993), anti-CYP2C9 in tienilic acid-induced hepatitis (Homberg et al. 1984; Robin et al. 1996), anti-CYP1A2 in dihydralazine-induced hepatitis (Bourdi et al. 1990), and anti-CYPs in aromatic anticonvulsant-induced hypersensitivities (Leeder et al. 1992) have been reported. However, it is not fully understood whether the autoantibodies are the causes or consequences of hepatotoxicity. Studies to clarify the possible involvement of autoantibodies in drug-induced hepatitis are limited because the appearance of autoantibodies can usually be seen only in humans. We recently reported that aldolase B, which is an enzyme predominantly localized in the liver and kidney (Penhoet et al. 1966), was detected as an autoantigen that reacted with antibodies in the sera from two patients with type II diabetes mellitus and troglitazone-induced liver dysfunction (Maniratanachote et al. 2005b). The titer of antialdolase B remained high for several weeks after stopping troglitazone administration. This finding supported the idea that troglitazone hepatotoxicity may have an immunological basis.

However, autoantibodies to aldolase B were also detected in the sera of patients with chronic hepatitis as well as liver cirrhosis (Brown et al. 1987; Maniratanachote et al. 2005b). There are several reactive metabolites generated by troglitazone (Fig. 2) (Kassahun et al. 2001; Tettey et al. 2001; Yamamoto et al. 2002). Aldolase B, which is an enzyme predominantly localized in the liver (Penhoet et al. 1966), may be one of the target proteins that interact with those reactive species and trigger the immune response. This study suggested that liver dysfunction might cause the appearance of autoantibodies to aldolase B, which may then aggravate the hepatitis. In addition, the antialdolase B titer might indicate the severity of liver dysfunction. Further studies will be needed to clarify the mechanisms of hypersensitivity reactions.

7 Mechanisms of Troglitazone-Induced Hepatotoxicity

Troglitazone has been shown to induce apoptosis in various hepatic (Bae and Song 2003; Tirmenstein et al. 2002; Yamamoto et al. 2001) and nonhepatic (Shiau et al. 2005) cell types depending on the concentration and duration of exposure. Unlike its pharmacological effects, the toxicity of troglitazone seems to be a PPAR γ-independent mechanism, and the higher affinity PPARγ agonists such as rosiglitazone and pioglitazone possess much lower toxic effects (Lehmann et al. 1995; Shiau et al. 2005). In addition, Shiau et al. (2005) demonstrated that a synthetic counterpart of troglitazone, which lacks PPARγ activation activity, was also able to induce apoptosis in cultured cells. A PPARγ-independent mechanism is also possible in human hepatocytes because the expression of PPARγ in normal human liver cells is very low (Green 1995), and rosiglitazone does not induce apoptosis (Toyoda et al. 2001). Troglitazone was shown to inhibit equally the proliferation of both $PPAR\gamma^{-/-}$ and $PPAR\gamma^{+/+}$ mouse embryonic stem cells (Palakurthi et al. 2001).

As mentioned above, M1, M2, and M3 metabolites are relatively stable, and the quinone metabolite, M3, has been suggested to be associated with troglitazone hepatotoxicity in humans (Neuschwander-Tetri et al. 1998). Although these metabolites showed lower toxic effects compared to the parent compound, troglitazone, when mammalian hepatocytes and hepatoma cell lines were treated directly (Tettey et al. 2001; Tirmenstein et al. 2002; Yamamoto et al. 2001, 2002), the possibility that the metabolites are toxic was not excluded due to the shortage of CYPs and other enzyme activities in the cells. In addition, when exposing the cells to these metabolites, they are unlikely to enter the cells in significant concentrations. On the other hand, it is most likely that troglitazone causes hepatic cell death via apoptosis. Caspase-3 was activated by troglitazone treatment, and pharmacological inhibition of caspase blocked troglitazone-induced cell death (Jung et al. 2007). Apoptosis is a normal physiologic form of cell death and plays a prominent role in liver pathogeneses such as autoimmune liver diseases, viral hepatitis, and drug-induced hepatitis. From this point of view, the cellular, molecular, and *in vivo* responses to troglitazone toxicity will be reviewed in the following sections.

7.1 Mitochondria-Mediated Toxicity

Mitochondria are known to be a source of reactive oxygen species (ROS), suggesting that a direct effect of troglitazone on mitochondrial physiology may play a role in hepatotoxicity (Narayanan et al. 2003). The development of troglitazone-induced toxicity in liver cells could be caused by a reduction of the mitochondrial membrane potential with a concomitant depletion of cellular ATP concentration (Bova et al. 2005; Tirmenstein et al. 2002). Subsequently, it increases the mitochondrial membrane permeability transition and calcium ion (Ca^{2+}) efflux (Masubuchi et al. 2006). The result of these effects on mitochondria is the release of cytochrome c into the cytoplasm and activation of caspases leading to apoptosis (Bova et al. 2005). Using immortalized human hepatocytes, Lim et al. (2008) found that troglitazone rapidly dissipated the mitochondrial inner transmembrane potential, followed by a shift of the redox ratio of mitochondrial thioredoxin-2 (Trx2) toward the oxidized state, and subsequent activation of apoptosis signal-regulating kinase 1 (Ask1). Ong et al. (2007) established heterozygous superoxide dismutase 2 hetero-knockout [Sod2(+/−)] mice as an experimental animal model of silent mitochondrial stress. They found that troglitazone caused liver injury in the high-dose (30 mg/kg/day, i.p.) group, manifested by an approximately twofold increase in serum ALT in Sod2(+/−) but not in wild-type mice. This mouse model could be useful to analyze the dynamics of mitochondrial changes *in vivo* and to investigate the involvement of reactive metabolites in mitochondrial toxicity. Thus, mitochondrial abnormalities could be one of the useful biomarkers of troglitazone-induced idiosyncratic hepatotoxicity.

7.2 Kinase-Mediated Cell Toxicity Pathway

The three well-characterized mammalian mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase (Erk), c-Jun N-terminal kinase (JNK), and p38 are regulated by phosphorylation and play important roles in a variety of cellular processes including growth, differentiation, and apoptosis (Johnson and Lapadat 2002). Erk is generally activated by mitogens, while JNK and p38 are preferentially activated by stress and inflammatory cytokines. The most obvious effect of troglitazone on apoptosis is likely via the promotion of JNK, which in turn activates c-Jun by phosphorylation as well as by activation of p38 (Bae and Song 2003). Gardner et al. (2005) and Jung et al. (2007) reported that calcium/calmodulin-dependent kinase II (CaMKII) is a critical regulator of double-stranded RNA-activated protein kinase (PKR)-dependent p38 and eukaryotic initiation factor 2α (eIF2α) phosphorylation in response to endoplasmic reticulum (ER) calcium depletion by troglitazone. Activation of these kinase-signaling pathways is PPAR γ-independent. In addition, troglitazone also causes the induction of Bax, Bad, the cleavage of Bid, and the release of cytochrome c. Moreover, the mitogen-activated protein kinase (MEK) 1/2-ERK1/2 signaling pathway may be implicated in the

growth inhibitory effect by troglitazone in human cancer cell lines (Motomura et al. 2005; Jung et al. 2007). JNK is characterized as a stress-activated protein kinase based on its activation in response to the inhibition of protein synthesis. These reports suggest that troglitazone induces apoptosis via a caspase-dependent mechanism associated with the downregulation of MEK/ERK and upregulation of p38.

Cyclin-dependent kinases (CDKs) are serine-threonine protein kinases that regulate cell cycle progression. These kinases are activated by various cyclins, inhibited by natural inhibitors such as p21, p27, and p18, and are tightly controlled by transcriptional and posttranscriptional modifications (Sherr and Roberts 1999). Bae et al. (2003) reported that troglitazone-induced cell cycle arrest by this pathway, and apoptosis of hepatoma cell lines ware caused G1 cell cycle arrest through the induction of p53 related proteins and the reduction of cyclin D1, phospho-RB and CDK activities.

7.3 Protein Translation-Associated Toxicity

The endoplasmic reticulum (ER) is a major site of protein synthesis, and its inside or lumen is a major site of protein folding (Gething and Sambrook 1992). In mammalian cells, naturally the rate of protein synthesis is rapidly reduced following the induction of apoptosis. The phosphorylation of eIF2α is important in the regulation of selective translation during ER stress and the unfolded protein response (Holcik and Sonenberg 2005). Troglitazone was shown to promote Ca^{2+} release from the ER leading to PERK and PKR activation, phosphorylation of eIF2α, translation inhibition, and growth arrest (Fan et al. 2004; Gardner et al. 2005).

It is known that the ER is a major cellular storage site of Ca^{2+} in the cell, and that ER chaperones play important roles in Ca^{2+} accumulation and release. Any disturbance in the ER homeostasis causes the release of Ca^{2+}, which in turn blocks ER protein processing. This results in the accumulation of incompletely folded proteins and activates the transcription of ER chaperone genes (Liu et al. 1998; Lodish and Kong 1990). We found that troglitazone treatment of hepatoma cell lines led to overexpression of immunoglobulin heavy chain binding protein (BiP), an abundant chaperone protein in the ER (Maniratanachote et al. 2005a). The important role of this chaperone protein was indicated by the phenotypic change in cell viability when BiP expression was inhibited by small interference RNA (Maniratanachote et al. 2005a). This condition rendered cells more susceptible to the toxic effects of troglitazone. Collectively, it might be postulated that troglitazone acts as a chemical stress signal that causes the release of Ca^{2+} from the ER, and that BiP expression is one of the cellular defense mechanisms of the ER in response to troglitazone-induced toxicity.

Ribosomal protein P0 (P0) was found to be one of the targets of troglitazone cytotoxicity in HepG2 cells (Maniratanachote et al. 2006). P0 is known as a phosphoprotein that functions in the protein translation process (Gonzalo et al. 2001). It was found that, rather than its overexpression, dephosphorylation of P0, which could not be prevented by caspase inhibition, occurred in troglitazone-induced cytotoxicity

(Maniratanachote et al. 2006). Although the dephosphorylation enzyme involved was not identified, a posttranslational modification, dephosphorylation, of P0 was suggested to be associated with the troglitazone-induced toxicity. Proteomics and system biology studies will provide new insights into troglitazone-induced toxicity.

8 Conclusions

Factors affecting the susceptibility to drug-induced hepatic injury include age, sex, co-administered drugs, genetic polymorophism, and enzyme activities catalyzing metabolic activation pathways. Idiosyncratic hepatotoxicity in human is usually unpredictable, pharmacologically independent, very rare, and not reproducible in experimental animal models, which makes it difficult to study (Lee 2003). Troglitazone is known as a typical cause of idiosyncratic hepatotoxicity and has been extensively studied for the past decade. Although a number of toxicological tests, both *in vivo* and in vitro, have been performed, no direct mechanism has been found that can explain why troglitazone hepatotoxicity occurred in only some individuals. We have learned from previous reports that the mechanism of troglitazone hepatotoxicity is PPARγ-independent, that the molecular mechanisms of apoptotic cell death are most likely involved in the hepatotoxicity, and that its idiosyncratic nature may be genetically determined.

Recent findings concerning the miRNA functions in specific tissues has enabled better understanding of the molecular mechanisms of various pathologies and diseases. Among several hundred miRNAs, we first reported the involvement of miRNA on the posttranscriptional regulation of CYPs (Tsuchiya et al. 2006). The decreased expression of miR-27b is one of the causes of the high expression of CYP1B1 protein in humans (Tsuchiya et al. 2006). In addition, we found that miR-148a posttranscriptionally regulated human hepatic pregnane X receptor, resulting in a modulation of the inducible and/or constitutive levels of CYP3A4 in human liver (Takagi et al. 2008). Therefore, studies on miRNAs and their targets could contribute to elucidating the mechanism of troglitazone-induced idiosyncratic hepatotoxicity.

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