Drug-induced hepatotoxic reactions may account for up to 30% of all adverse drug reactions, and because of their unpredictable and idiosyncratic nature, these reactions are a constant problem in the drug development process and in clinical practice. Although many studies are performed before clinical trials and marketing, such reactions still occur in some individuals. Most hepatotoxicants are thought to produce chemically reactive metabolites, which covalently bind to endogenous macromolecules, and are simultaneously inactivated by various scavenger enzymes.

A class of compounds named thiazolidinediones (troglitazone, rosiglitazone and pioglitazone) was put on the market as new synthetic ligands of the peroxisome proliferator-activated receptor γ (PPARγ) for the treatment of insulin-resistant diabetes mellitus. Troglitazone was withdrawn from the market in 2000 due to idiosyncratic hepatotoxicity in human. This toxicity was unpredictable, pharmacologically independent, rare, and not reproducible in experimental animals.

Differing from other thiazolidinediones, troglitazone contains a chroman ring of vitamin E. This structure, however, has the potential to undergo metabolic activation to form troglitazone quinone or metabolite M3 by CYP3A4 and CYP2C81). In human, it is likely that CYP3A4 is primarily responsible for this reaction. In addition, troglitazone has been shown to induce CYP3A in human and rat hepatocytes, which stimulate the formation of the quinone. By the action of CYP3A, troglitazone as well as troglitazone quinone yields several reactive intermediates2). In vitro, the formation of an epoxide of troglitazone quinone biotransformed by CYP3A4 was also identified3). It is known that quinones represent a class of toxicological intermediates that are involved in acute cytotoxicity and immunotoxicity as well as carcinogenesis. Gene analyses demonstrated that 40% of the case patients with an abnormal elevation of liver enzymes caused by troglitazone treatment possessed the null genotype of both CSTT1 and GSTT14). Hence, interindvidual differences in the scavenger enzymes might contribute to the susceptibility and individual risk for troglitazone hepatotoxicity. However, the complete mechanism is still largely unknown.

Idiosyncratic hepatotoxicity is usually accompanied by immune-mediated hypersensitivity reactions. We identified that aldolase B was detected as an autoantigen that reacted with antibodies in sera from patients with troglitazone-induced liver dysfunction5). The titer of anti-aldolase B remained high for several weeks after stopping troglitazone administration. However, at present a definitive explanation concerning the occurrence of aldolase B autoantibody, either as a cause or consequence of the progression of hepatotoxicity, is still lacking.

Troglitazone may serve as a stress signal to the ER membrane, which in turn causes the overproduction of immunoglobulin heavy chain binding protein (BiP). We found that BiP was overexpressed by troglitazone treatment6). The important role of this chaperone protein was demonstrated by the phenotypic change in cell viability when BiP expression was inhibited by small interference RNA6). This condition rendered cells more susceptible to the toxic effects of troglitazone. With respect to the inhibition of translation by troglitazone toxicity, we recently found that dephosphorylation of ribosomal protein P0 (P0) also occurred in troglitazone-induced cytotoxicity7). Therefore, dephosphorylation of P0 may play a role in the regulation of protein translation in response to the toxic effects of troglitazone.

Taking those results into consideration, the mechanism of troglitazone hepatotoxicity is PPARγ-independent, the molecular mechanisms of apoptotic cell death are most likely involved in the hepatotoxicity, and the idiosyncratic hepatotoxicity might be a consequence of a genetic basis in susceptible individuals.