IN VITRO STUDY OF THE MECHANISMS OF TERBINAFINE ASSOCIATED HEPATIC INJURY
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[Purpose] Oral antifungal terbinafine has been reported to induce inflammatory responses that cause idiosyncratic liver injury. However, the underlying mechanism remains unknown. To examine the inflammatory reactions leading to hepatic injury, we investigated whether terbinafine and other antifungal drugs increase the release of pro-inflammatory cytokines and chemokines using human monocytic cells.

[Methods] The release of interleukin (IL)-8 and tumor necrosis factor (TNF) α from human monocytic THP-1 and HL-60 cells was measured. Phosphorylation of extracellular signal-regulated kinase (ERK) 1/2, p38 mitogen-activated protein (MAP) kinase and c-Jun N-terminal kinase (JNK) 1/2 in THP-1 cells was investigated.

[Results and Discussion] The release of IL-8 and TNF α from human monocytic THP-1 and HL-60 cells was significantly increased by treatment with terbinafine or butenafine but not by fluconazole, suggesting that terbinafine and its structurally similar drugs can stimulate monocytes and increase the release of pro-inflammatory cytokines. Terbinafine also significantly increased the phosphorylation of extracellular ERK1/2 and p38 MAP kinase in THP-1 cells. Pretreatment with a MAP kinase/ERK kinase (MEK) 1/2 inhibitor U0126 significantly suppressed the increase of IL-8 and TNF α levels by terbinafine treatment in THP-1 cells, but p38 MAPK inhibitor SB203580 or JNK1/2 inhibitor SP600125 did not. These results suggested that an ERK1/2 pathway plays an important role in the release of IL-8 and TNF α in THP-1 cells treated with terbinafine.

[Conclusions] We demonstrated that the release of inflammatory mediators caused by terbinafine might be one of the mechanisms underlying immune-mediated liver injury. This in vitro method may be useful to predict adverse inflammatory reactions that lead to hepatic injury.

THE IMPORTANCE OF ISOFORMS OF GLUTATHIONE S TRANSFERASES IN THE PROTECTION FROM DRUG-INDUCED HEPATOTOXICITY
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[Purpose] Some clinical studies have indicated that the genetic deletion of GST (glutathione-S-transferase) M1 and T1 is one of the risk factors of drug-induced hepatotoxicity. The purpose of our research is to demonstrate this hypothesis by measuring the protein amount covalently bound to reactive metabolites in a series of in vitro experiments.

[Methods] We established an experimental system to detect cytosol-mediated suppression of the covalent binding of [14C]-troglitazone to microsomal proteins by incubating [14C]-troglitazone with liver microsome and cytosol fractions. To investigate the role of each GST isoform in their glutathione conjugation, recombinant GST proteins were also used instead of liver cytosol.

[Results and Discussion] The covalent binding of [14C]-troglitazone was increased by the metabolic activation with mouse liver microsome and it was significantly decreased by the addition of mouse liver cytosol, suggesting that GSTs in cytosol promote the detoxification of active metabolites of troglitazone by facilitating their glutathione conjugation. Furthermore, recombinant GSTA1, M1 and T1 could decrease its covalent binding.

[Conclusions] Our in vitro results suggest that GSTs can suppress the covalent binding of troglitazone to microsomal proteins. We are now investigating which GST isoforms are mainly involved in the detoxification of the reactive metabolites of troglitazone in the liver.