Cellular and animal models for human drug-induced liver injury

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Drug-induced liver injury (DILI) is one of the most common reasons for the discontinuation of drug discovery and the withdrawal of approved drugs from the market, but it is difficult to predict whether DILI will occur in humans based on current preclinical safety evaluations using experimental animals and/or cell-based in vitro assays. On the basis of the accumulating recent knowledge of immune systems in hepatic pathology, immune-mediated DILI is recognized to cause an imbalance of differentiated T cells. We reported the relationship between expression changes of Th cell-related factors and DILI in our established mouse models of halothane (HAL), phenytoin, dicloxacillin, diclofenac, carbamazepine, flutamide, and methimazole (MTZ).

Recently, study on circulating microRNAs (miRNAs) as potential biomarkers of DILI has received increasing attention. It has been demonstrated that miR-122 and miR-192, which are liver enriched, could be potential biomarkers of DILI. However, these miRNAs cannot discern types of injuries.

We investigated role of miRNAs in HAL- and MTZ-induced liver injury in mice. Among the predicted targets, we discovered that a signal transducer and activator of transcription 3 (STAT3) was particularly up-regulated during the early phase of HAL-induced liver injury. The suppressed miR-106b expression, as well as the subsequent up-regulation of STAT3, was critical for the pathogenesis of HAL-induced liver injury. Among targets of miRNAs in MTZ-induced liver injury, down-regulation of Th2 suppressive transcriptional factor, such as SRY-related HMG-box 4 (SOX4) and lymphoid enhancer factor-1 (LEF1) were seen from the early phase of liver injury. Thus, negative regulations of the expression of SOX4 by miR-29b-1-5p and that of LEF1 by miR-449a-5p are suggested to play an important role for development of Th2 bias in MTZ-induced liver injury. Studies on the plasma miRNAs that can distinguish different types of DILI, hepatocellular injury, cholestasis and steatosis, with next generation high-throughput sequencing will also be introduced. The present studies provide important information to understand the mechanism of DILI and also provides new insight into development of predictive biomarkers for immune- and inflammation-related DILI.