Editorial

Stem Cell INVESTIGATION

miRNA-324, a potential therapeutic target for paracetamol-induced liver injury

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Paracetamol is one of the most widely used medications for relieving pain and fever. When taken in the therapeutic doses, paracetamol is predominantly metabolized in the liver via conjugation reaction by phase II drug metabolizing enzymes such as sulfotransferases and glucuronyl transferases, and is removed from the body without liver damage (1). However, when paracetamol is taken in excessive doses, it is bioactivated by phase I enzymes (e.g., CYP3A4 and CYP2E1) to generate a toxic intermediate N-acetyl-p-benzoquinone imine (NAPQI). Rapid generation of NAPQI can lead to the depletion of intrahepatic glutathione and result in hepatocyte death and liver injury (2). Thus, hepatotoxicity elicited by paracetamol overdose is the most common cause of poisoning-related deaths (3). In other studies, overdose of paracetamol accounted for the highest proportion of cases of acute liver failure in many developed countries, resulting in death or liver transplantation (4,5). Currently, N-acetylcysteine (NAC) is the mainstay strategy in treating hepatotoxicity following paracetamol overdose. However, oral and intravenous NAC treatment has limitations because of adverse effects (6,7). Thus, identifying new therapeutic targets would be of help for clinical remedy of paracetamol overdose-related liver injury.

Numerous studies have been conducted on the expression and function of drug-metabolizing enzymes (DMEs), and the information was applied for better understanding and prediction of drug responses in patients (8). Moreover, identification of novel regulators of DMEs is critical to supply more information for clinical applications. In a recent issue of *Stem Cells Transl Med*, Hay and colleagues have identified that inhibition of a novel noncoding RNA can reduce paracetamol-induced liver toxicity (9). The authors demonstrated that miRNA-324-5p regulates phase II drug metabolism and that the inhibitor of miRNA-324-5p can promote nontoxic metabolism of paracetamol. This finding has the potential to help clinical research in identifying future therapeutic strategy for paracetamol-induced toxicity.

To examine hepatocyte biology *in vitro*, immortalized human hepatocytes have been developed since they are the most physiologically relevant to human liver in drug response (10). However, some limitations such as karyotypic instability and poor function exist in the derived cell lines, thus preventing their further application (10). Previously, Hay *et al*. have used human embryonic stem cells (hESCs) to generate human hepatocyte-like cells (hHLCs) using a serum-free-based procedure (11), which has been proved to be scalable and more primary in nature and is promising in modeling human drug metabolism and toxicity. In the current research, according to the established methodology, hESCs were differentiated to hHLCs through 18 days of culture, as indicated by the appropriate cell morphology, gene expression, and appreciable levels of metabolic function (9). Hay *et al*. compared hHLCs with adult human hepatocytes and confirmed the gene expression profiles of phase I, II and II drug-metabolism (9). Thus, use of hESCs and hHLCs has become a useful *in vitro* model in studying and understanding the genotype-phenotype relationship in the human population.

The miRNAs post-transcriptionally control protein expression by binding to the 3'-UTRs of target mRNAs, and thereby lead to translational inhibition or mRNA

degradation (12). In many laboratories, miRNAs have been shown to affect DMEs related with paracetamol metabolism (13-19). For example, miR-27b and miR-378 regulate paracetamol oxidation enzyme CYP3A4 and CYP2E1, respectively (13,14). Research on miRNAs regulation of phase II enzymes was limited to SULT1A1 (paracetamol sulfation enzyme), GSTP1 (NAPQI conjugation enzyme) and UGT1A (paracetamol glucuronidation enzyme) (15-17). Other studies have focused on miRNA regulation of paracetamol transporter-related ATP Binding Cassette (ABC) transporters (e.g., ABCC4 and ABCG2) (18,19). In the current study, Hay and colleagues enlarged our understanding on the information of miRNA that can regulate paracetamol-metabolizing DMEs by identifying a novel miRNA, miRNA-324-5p, in the regulation of SULT2A1 (9). They elucidated a supportive role of antagomir 324 (miR-324 inhibitor) in the improvement of hepatocyte survival in the context of acute injury and patient recovery after paracetamol overdose. From a standpoint of molecular mechanisms responsible for hepatotoxicity following paracetamol overdose, this study broadens our understanding on miRNA-based regulation of phase II drug metabolizing enzymes and may offer a new and attractive strategy for the treatment of liver injury induced by paracetamol overdose.

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Footnote

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