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Reducing hepatocyte injury and necrosis in response to paracetamol using non-coding RNAs

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The authors have no conflict of interest to declare.
Author’s contributions:

Dagmara Szkolnicka: Conception and design; collection and/or assembly of data, data analysis and interpretation; manuscript writing and proof-reading.

Baltasar Lucendo-Villarin: collection and/or assembly of data, data analysis and interpretation

Kenneth Simpson: provision of patient samples, data analysis and interpretation, manuscript proof reading.

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Stuart J Forbes: supervision, data analysis and interpretation, manuscript proof reading.

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Key words:

Drug induced liver injury; micro RNA, hepatocyte, apoptosis, necrosis, paracetamol.
ABSTRACT

The liver performs multiple functions within the human body. The liver is composed of numerous cell types which play important roles in organ physiology. Our study centres on the major metabolic cell type of the liver, the hepatocyte, and its susceptibility to damage during drug overdose. In these studies hepatocytes were generated from a renewable and genetically defined stem cell resource. In vitro derived hepatocytes were extensively profiled and exposed to varying levels of paracetamol and plasma isolated from liver failure patients, with a view to identifying non-coding micro-RNAs which could reduce drug or serum induced hepatotoxicity. We identified a novel anti-microRNA which reduced paracetamol induced hepatotoxicity and glutathione depletion. Additionally, we also demonstrated a pro-survival role for anti-microRNA-324 in response to plasma collected from liver failure patients. We believe that these studies represent an important advance for the field, demonstrating the power of stem cell derived systems to model human biology ‘in a dish’ and identify novel non-coding microRNAs which could be translated to the clinic in the future.
INTRODUCTION

The liver is a multi-functional and highly regenerative organ. In both the acute and chronic settings liver disease has dire consequences for health. A common cause of liver damage is adverse reactions to drugs which can lead to drug induced liver injury (DILI). This creates major problems for patients, clinicians, the pharmaceutical industry and regulatory authorities (Olsen and Whalen, 2009). It has been reported that in the United Kingdom (UK) approximately 15% of the hospital in-patients suffer from liver toxicity in response to medicines during admissions, with 20% of these patients readmitted again after one year and a 2% mortality rate (Davies et al, 2009, Davies et al, 2010;). The annual cost to the National Health Service in the UK ~£450 million with the costs growing year by year (Pirmohamed, 2004).

In the context of drug overdose or serious adverse reactions, liver failure can be acute and life threatening, and in some cases require orthotopic liver transplantation. While transplantation is highly successful, such an approach has many limitations (Szkolnicka et al 2014a) and justifies basic science attempts to develop better human models to study liver injury and cost effective and scalable intervention strategies. With this in mind, we have studied the importance of microRNAs (miRs) in regulating human drug metabolism and their potential to reduce liver toxicity in response to toxic levels of paracetamol.

miRs are small non-coding RNAs that are approximately 20 - 24 nucleotides long and their major function is to fine tune gene expression of target their genes. Enzyme processing of primary and precursor microRNAs generates a mature microRNA that is incorporated to the RNA-induced silencing complex (RISC). The complex recognizes the target mRNA through perfect and imperfect base pairing with the target miRs (Bartel, 2009). Recently, it has been demonstrated that microRNAs play a role in regulating the first phase of drug metabolism (Pan et al, 2009a; Tsuchiya et al, 2006; Yu, 2009; Yu and Pan, 2012) as well as play an
essential role in controlling phase III transporters important in drug efflux (Kovalchuk et al, 2008; Zhu et al, 2008). However the second phase of drug metabolism, drug conjugation, has not been studied in detail. Drug conjugation is crucial in human drug metabolism, and any alternations in this process can lead to massive hepatocyte death and acute liver failure, which can be life threatening. To test the importance of miRs in regulating phase II drug metabolism we opted to study the metabolism of a commonly used analgesic, paracetamol. When taken in the appropriate amounts paracetamol is modified by sulfuryl transferases and UDP glucuronosyl transferases and removed from the body without organ damage (Chun et al, 2009). However, when paracetamol is taken above the recommended dose it is metabolised by phase I enzymes to generate a toxic intermediate N-acetyl-p-benzoquinone imine (NAPQI), which if untreated can lead to hepatocyte cell death and liver failure, placing the patient in a life threatening situation. In order to promote non-toxic drug metabolism, in the context of drug overdose, we identified and employed candidate miRs to regulate the different steps of paracetamol metabolism.

In summary, we have identified a novel microRNA which regulates phase II drug metabolism promoting non-toxic paracetamol drug metabolism, thereby reducing hepatic cytotoxicity. Moreover, we demonstrate a supportive role for microRNAs in managing the toxic nature of human liver failure plasma. We believe our findings are novel and provide proof of concept. These studies exemplify the power of pluripotent stem cell derived models ‘in a dish’ to identify new approaches to treating human liver damage.
METHODS AND MATERIALS

Cell Culture and Differentiation

hESCs (H9) were cultured as described in (Hay et al, 2008; Hay et al, 2011) and maintained in a humidified 37 °C, 5% CO₂ incubator. The cells were differentiated as described previously (Szkolnicka et al, 2014a; Szkolnicka et al, 2014b).

Primary Human Hepatocyte Culture

The cryopreserved human primary hepatocytes were purchased from Life Technologies. In this study, female line (Hu8119; HMCPIS) and male line (Hu8182; HMCPIS) were chosen. Both lines were donated from Caucasian patients of 21-27 years of age. The cryoplateable hepatocytes were plated and maintained as per vendor’s instruction. Briefly, hepatocytes were resuspended in thawing medium (CM3000) and plated onto matrigel in a 48-well plates. Subsequently, cells were placed in the incubator at 37°C (5% CO₂) for 24 hours. At 24 hours post-replating, the medium was changed to incubation medium (CM4000). At 48 hours post-replating, hepatocyte metabolic activity (CYP3A and CYP1A2) were measured using Promega luciferase-based assay.

RNA Isolation and Quantitative Polymerase Chain Reaction for SULT2A1 and GSTT1

The RNA was isolated, reversely transcribed and used for TaqMan polymerase chain reaction as described in Szkolnicka et al (2014a). The reference numbers of particular primers can be found in Supplementary Table 4.
**RT² Profiler PCR Array**

The total RNA of hESC-derived hepatocytes (day 18) and Primary Human Hepatocytes (purchased from 3H Biomedical AB, Sweden) was reverse transcribed using RT² First Strand Kit (QIAGEN) as per manufacturer’s instructions. The qPCR reaction was set up using RT² Profiler PCR Array (Human Drug Metabolism Array, Human Drug Metabolism Phase II Enzymes Array, and Human Drug Transporters Array were purchased from QIAGEN) as per manufacturer’s instructions.

**MicroRNA Profiling**

The total RNA of hES-derived hepatocytes (day 18; n=3) and Primary Human Hepatocytes (purchased from 3H Biomedical AB) were analysed on Agilent miRNA platform (using Agilent’s SurePrint G3 Human v16 microRNA 8x60K microarray slides; miRBase version 16.0) following Sistemic proprietary SOPs. One 100 ng of total RNA, from a working solution at 50ng / ul in nuclease-free water, was used as input for each microarray experiment. Each slide contained 8 individual arrays, each array was identified by a unique barcode and contained capture probes for 1349 microRNAs (1205 Human; 144 viral). The microarray data were normalized using Sistemic’s in-house pre-processing and data quality control (QC) methods. Detection calls (present or absent) for individual miRNAs were compared across the samples. The detection calls were calculated using the Agilent Feature Extraction (AFE) software version 10.7.3.1. A detailed description of how these calls are made is available in the Feature Extraction Reference Guide on the Agilent website (http://www.genomics.agilent.com)
**MiR – mRNA Binding Analysis**

TargetScanHuman6.2 is an online tool that predicts microRNA binding sites at the 3’UTR of the biological target. The programme focuses on the presence of conserved and non-conserved sites that match the seed region of each microRNA (Lewis *et al*, 2005).

**Immunofluorescence**

Cell cultures at day 18 of cellular differentiation were fixed in 100% ice-cold methanol at -20°C for 30 minutes. After fixation, cell cultures were washed twice with PBS at room temperature. Cells were blocked with 0.1% PBS-Tween containing 10% BSA for 1 hour and subsequently incubated with primary antibodies diluted in PBS-0.1% Tween/1% BSA (the GSTT1 antibody was diluted in PBS-0.1% Tween/2% BSA) at 4°C overnight. The following day, the primary antibody was removed, and the fixed monolayers were washed three times with PBS-0.1% Tween/1% BSA (the GSTT1 antibody was washed in PBS-0.1% Tween/2% BSA). Following this, the cells were incubated with the appropriate secondary antibody diluted in PBS for 1 hour at room temperature and washed three times with PBS. After washing, the Hoechst 33342 (NucBlue® Live Cell Stain Ready Probes; Life Technologies) diluted in PBS (as per manufacturer’s instructions) was added to the culture and incubated for 20 minutes at room temperature. Subsequently, the solution was removed and cell cultures were mounted with Mountant PermaFluor (Thermo Scientific). The cells were analyzed by Olympus TH4-200 microscope and Volocity 4 software. The percentage of positive cells and standard deviation were estimated from at least four random fields of view and quoted as ± standard error. The list of antibodies and dilutions are provided in Supplementary Table 4.
Paracetamol – Induced Toxicity (Toxicity Testing)

Paracetamol (Sigma-Aldrich) was diluted in ethanol (Sigma-Aldrich) and prepared at 0.5 M stock concentration. Different paracetamol concentrations (0 mM, 1 mM, 2 mM, 5 mM, 10 mM, 20 mM, and 50 mM) were prepared by diluting the stock solution in specific volumes of HepatoZYME™ supplemented with factors (10 ng/ml HGF; 20 ng/ml OSM) and 2% Bovine Serum Albumin (Sigma-Aldrich). At day 17, cells were treated with specific drug concentration and left for 24 hours in the incubator at 37°C. At day 18 ATP production was measured by the CellTiter®-Glo (Promega). For primary human hepatocytes, the cells were treated with the same range of paracetamol concentrations as above at 48 hours post-replating. The concentrations were prepared by diluting the stock solution in specific volumes of incubation medium (CM4000) and 2% Bovine Serum Albumin (Sigma – Aldrich). Cells were incubated with the drug for 24 hours at 37°C. Subsequently, ATP production was measured by the CellTiter®-Glo (Promega).

In Vitro Modulation of Paracetamol Toxicity by MicroRNAs

At day 17, cells were transfected with scrambled controls or antagomirs to miR-24, miR-324 for 24 hours at 37 °C. Once transfected, hESC-derived hepatocytes were exposed to the concentration of paracetamol resulting in 50% death (IC50) for another 24 hours. At day 19, the toxic effect of the drug was measured using CellTiter – Glo® Luminescent Cell Viability Assay (Promega) and GSH/GSSG-Glo™ Assay (Promega).
In Vitro Modulation of Paracetamol Toxicity by N-acetylcysteine (NAC)

N-acetylcysteine (NAC; Sigma –Aldrich) was diluted in sterile water and prepared at 1M concentration. At day 17, hESC-derived hepatocytes were treated with 1mM NAC (optimal concentration determined from a range of 0-1.25mM) diluted in specific volumes of HepatoZYME™ supplemented with factors (10ng/ml HGF; 20 ng/ml OSM). At day 17, cells were treated with specific drug concentration and left for 24 hours in the incubator at 37°C. At day 18 the paracetamol toxicity was measured by the CellTiter®-Glo Luminescent Cell Viability Assay from Promega.

Cell Viability Assay

Cellular ATP levels were measured using CellTiter – Glo® Luminescent Cell Viability Assay (Promega) as per manufacturer’s instructions and the luminescence signal was detected by the luminometer (Promega; Madison, WI, http://www.promega.com). The IC50 (the concentration of the compound resulting in 50% death) of paracetamol (APAP) was estimated from the function f(x) = ax + b.

Reduced Glutathione Depletion Assay

The amount of reduced glutathione produced in the hESC-derived hepatocytes was measured by GSH/GSSG-Glo™ Assay from Promega (Madison, WI) and carried out as per the manufacturer’s instructions (http://http://www.promega.com/tbs/tb325/tb325.pdf).
**Patient Information, Sample Collection, Processing**

Ethical approval for the study was from the Scotland ‘A’ Research and Ethics Committee and written informed consent was obtained. Three female donors or their nominated next of kin consented to blood sampling. Paracetamol hepatotoxicity was prospectively defined as previously described (Craig *et al.*, 2013). Peripheral blood samples were obtained on the day of admission to the Scottish Liver Transplantation Unit. Serum was collected after centrifuging of blood samples at 1000 g for 15 minutes and 4 °C within 1 hour following collection, immediately aliquoted and stored and -80 °C until thawing for the experiments. Importantly, no paracetamol was detectable in the serum samples used in the study. Patient blood biochemistry and normal ranges are provided in Supplementary Table 5.

**Supplemental Information**

Supplemental information includes 5 figures and 5 tables.
RESULTS

**Defining Metabolic Gene Expression in Stem Cell Derived Hepatocytes.**

hESC-derived hepatocytes were produced *in vitro* using established methodology (Szkolnicka *et al*, 2014a, Szkolnicka *et al*, 2014b) and demonstrated appropriate cell morphology, expression of liver transcripts and displayed appreciable levels of metabolic function (Figure 1 A-C). Cyp3A activity in stem cell derived hepatocytes was estimated at 8.4% of the female and 22% of male adult hepatocytes (Figure 1C; Supplementary Figure 1). Whereas, Cyp1A2 activity was estimated to be 0.009% and 0.06% of female and male hepatocytes respectively (Figure 1C; Supplementary Figure 1). Post validation, stem cell derived hepatocytes were characterised for drug metabolising gene expression using microarray technology. Throughout these studies, stem cell derived hepatocytes were compared to freshly isolated primary human hepatocytes. From these studies we demonstrated that stem cell derived hepatocytes expressed transcripts for phase I, II and III drug metabolism, albeit at reduced levels in comparison to primary hepatocytes (Figure 2; Supplementary Table 1).

**Detailed Study of Paracetamol Metabolism in Stem Cell Derived Hepatocytes.**

In order to ascertain which metabolic pathways were intact, the data from the array experiments were analysed using Pharma KGB software (www.pharmgkb.org). From the analysis we determined that a number of metabolic pathways were intact in our stem cell derived system, including paracetamol metabolism (Supplementary Figure 2). When paracetamol is taken within the therapeutic range it is metabolised and excreted normally by phase II and III enzymes (Supplementary Figure 2). However, if the drug is taken at higher doses than recommended, phase I enzymes generate N-acetyl-p-benzoquinone imine
(NAPQI) which is toxic and leads to glutathione depletion and ultimately cell death (Supplementary Figure 2). The results generated from the array experiments were validated by immunostaining, focusing on key phase II and phase III proteins. Phase II enzymes from the non-toxic pathway, SULT2A1, and toxic pathway, GSTT1, were expressed in 59% and ~98% cells respectively (Figure 3A; Supplementary Table 1). Importantly, stem cell derived hepatocytes also expressed phase III drug transporters important in each pathway. Approximately 52% and 77% of cells expressed ABCG2 and ABCC1 respectively (Figure 3A; Supplementary Table 1). We therefore hypothesised that stem cell derived hepatocytes possessed the correct machinery to process paracetamol in a non-toxic and toxic manner (Figure 3B). To test this we exposed stem cell derived hepatocytes to a range of concentrations of paracetamol, ranging from 0 to 50 mM. Following exposure, cell viability was monitored by ATP production. From these studies we demonstrated that stem cell derived hepatocyte cell death increased in a dose dependent fashion with an IC50 value of 12.85 mM. Although differences in cytochrome P450 metabolic capacity were identified between stem cell derived hepatocytes and primary hepatocytes, the paracetamol IC50 values obtained in vitro were comparable to both female and male hepatocytes, 10.51 mM and 12.6 mM respectively (Supplementary Figure 3).

**Identification of Novel MicroRNAs Within Stem Cell Derived Hepatocytes**

Once we had established that stem cell derived hepatocytes responded to paracetamol appropriately, we wished to study microRNA (miR) expression within stem cell derived hepatocytes. miRs are known to be potent regulators of gene expression, and our hypothesis was that miRs could play an important role in modulating paracetamol metabolism and therefore drug overdose in hepatocytes. To screen for miRs which regulate this process, day 18 hESC-derived hepatocytes were harvested and analysed using Agilent miRNA platform.
From these studies we determined that stem cell derived hepatocytes and primary human hepatocytes expressed 367 miRs in common, with 220 miRs being expressed at similar levels and 147 miRs differentially expressed (Figure 4A and B; Supplementary Table 2). Of note, the major miR expressed in the liver, miR-122, was expressed at similar levels between primary and hESC derived hepatocytes (Figure 4C). Next, we evaluated similarly expressed miRs using TargetScanHuman6.2 (www.targetscan.org) to predict novel miRs which may regulate phase II enzymes important in paracetamol metabolism. The ‘hits’ from our screen were ranked based on the predicted efficacy using the context + scores (Friedman et al, 2009 and Grimson et al, 2007). Our analysis predicted that miR 24 and 324 could potentially regulate GSTT1 and SULT2A1 respectively, and those miRs served as the focus of further experimentation (Supplementary Table 3).

**MicroRNA 324 Regulates Paracetamol Induced Toxicity in Stem Cell Derived Hepatocytes**

In order to test our hypothesis that stem cell derived hepatocyte susceptibility to paracetamol overdose could be regulated by miRs, we transfected synthetic inhibitory non-coding RNAs. Stem cell derived hepatocyte transfection was optimised and miRs and antagomirs were used at a concentration of 50 nM for 24 hours prior to incubation with a toxic dose of paracetamol. In order to examine the effects of antagomir transfection on phase II enzyme expression, we performed qPCR and immunostaining. hESC-derived hepatocytes transfected with the scrambled control served as our baseline throughout. In response to transfection with the antagomir for miR 324, stem cell derived hepatocytes expressed greater SULT2A1 gene and protein expression. (Figure 5A and B). In contrast, transfection with miR-324 or the non-coding RNAs for miR-24 did not result in gene expression changes, nor dramatic alterations in cell viability and reduced glutathione levels (Supplementary Figures 4 and 5). Once we had established that SULT2A1 expression could be modulated successfully, we measured cell
viability in response to a 50% toxic dose of paracetamol for 24 hours, by measuring ATP
depletion (IC50). The fold increase in cell viability was comparable with the cell viability
enhanced by N-acetylcysteine (NAC) (Figure 5C). Notably increased cell viability was
paralleled by a two fold increase in reduced glutathione levels (Figure 5D).

MicroRNA 324 Reduces Cell Necrosis in Response to Plasma from a Patient With
Fulminant Hepatic Failure.

Following on from acute paracetamol induced hepatocyte injury, we studied the toxic nature
of patient’s derived plasma on stem cell derived hepatocytes. As before stem cell derived
hepatocytes were differentiated and transfected with either the scrambled control or the
antagomir for miR-324. Twenty four hours post transfection, stem cell derived hepatocytes
were incubated with human plasma from three female donors (anonymised patient details and
blood biochemistry is supplied in Supplementary Table 5). Following exposure to plasma,
stem cell derived hepatocyte ATP levels were measured. Notably, stem cell derived
hepatocytes transfected with antagomir 324 displayed greater levels of ATP which was
significantly increased over scrambled controls in two out of three patients (Figure 6A). In
line with ATP, we also measured caspase 3 and 7 activity in stem cell derived hepatocytes.
As for ATP, we also observed a significant increase in caspase activity following transfection
with antagomir 324 in two out of three patients (Figure 6B). Taken together these data
suggest that increasing the levels of SULT2A1 gene expression redirected cell necrosis to
apoptosis, following challenge with plasma from patient with fulminant hepatic failure.
DISCUSSION

Despite major progress in the knowledge and management of human liver injury, there are approximately 2000 cases per year of acute liver failure (ALF) in the United States (Hoofnagle, 1995; Polson et al 2005; Fontana, 2008). Paracetamol overdose is a major cause of ALF, with critical damage done to the hepatocyte compartment of the liver, and accounts for approximately 50% of cases (Nourjah et al, 2006; Bari and Fontana, 2014). Although hepatocyte cell death occurs in large numbers, the manner by which the cells die following overdose remains complicated and controversial (Jaeschke et al 2012).

The hepatotoxic dose of paracetamol is considered to be greater than 75mg/kg. This translates into toxic blood concentrations that range between 25-150 mg/l (Winek, 1994 and Dollery, 1993). Currently, treatment with N-acetylcysteine (NAC) is the most effective strategy in treating paracetamol-induced liver injury. Patients that have ingested 75-150 mg/kg/24h can be considered for NAC treatment, with NAC usually prescribed if > 150mg/kg was ingested within 24 hours (based on the guidelines issued by the National Poisons Information Service UK; www.npis.com). Although successful, oral and intravenous NAC treatment may elicit serious side effects (Harrison et al, 1990; Bailey and McGuigan, 1998; Appleboam et al, 2002; Pakravan et al, 2008) and therefore new approaches to treat acute intoxication are necessary. In order to study the important nature of microRNAs in human drug toxicity, reliable and renewable liver models are required. In this vein, we have employed pluripotent stem cells to generate human hepatocyte like cells. The in vitro model employed in these studies is serum free and has already which has demonstrated promise in modelling human drug metabolism and toxicity testing (Szkolnicka et al, 2014a; Szkolnicka et al, 2014b; Medine et al, 2013; Zhou et al, 2014, Cameron, et al 2015). Moreover, in these studies we
support those observations as stem cell derived hepatocytes display similar IC50 values to male and female primary hepatocytes (Supplementary Figure 3).

MicroRNAs are potent non-coding RNAs which can alter mammalian gene expression and therefore represent promising candidates for modulating enzymatic pathways (Pan et al., 2009a; Tsuchiya et al., 2006; Yu, 2009; Yu et al., 2010; Yu and Pan, 2012; Kovalchuk et al., 2008; Zhu et al., 2008) and treating human disease. Several studies have shown that regulation of different microRNAs may potentially serve as effective therapeutics (Thong et al., 2014; Heidet and Gubler, 2009, Daige et al., 2014). In the recent years there has been a focus on miR regulation of phase I enzymes involved in human drug metabolism. Studies have demonstrated that miR-27b regulates CYP3A4 and CYP1B1 and miR-126* controls CYP2A3 expression (Pan et al., 2009a; Tsuchiya et al., 2006; Kalscheuer et al., 2008). Other studies have also focused on microRNA regulation of drug transporters such as P-glycoprotein and breast cancer resistant protein (Kovalchuk et al., 2008; Zhu et al., 2008; Liao et al., 2008; To et al., 2008, Pan et al., 2009b). While phase I and phase III of drug metabolism have been studied, there is still little known about regulation of phase II enzymes by microRNAs. Phase II enzymes, such as glutathione-s-transferases (GSTs) and sulfotransferases (SULTs), are essential to sufficiently detoxify different xenobiotics, therefore these enzymes serve as important clinical targets. In order to test whether microRNAs could potentially regulate phase II enzymes (SULT2A1 and GSTT1) that play an important role in paracetamol metabolism, we used TargetScan Human software to determine precise miR-gene binding interactions and used lipofectamine-based transfection to examine their supportive effects. Inhibition of miR-324-5p in hESC-derived hepatocytes resulted in increased SULT2A1 expression (Figure 5A and 5B). This led to improved cell survival in vitro, in a matter comparable with current clinical practice, NAC administration (Figure 5C).
Notably, the inhibition of miR-324-5p was paralleled by an increase in reduced glutathione production (Figure 5D). In contrast, inhibition of miR-24-3p did not have any effect on GSTT1 expression, cell viability and reduced glutathione production in the paracetamol studies. Although TargetScan has been widely used, and is considered to be the most effective in predicting miR-target binding sites (Baek et al, 2008; Witkos et al, 2011), algorithm prone errors may have led to this false prediction.

Given the promising effects of the antagomir 324 delivery in response to paracetamol, we were keen to assess its efficacy after exposure to liver failure serum from paracetamol poisoned female patients. Importantly, paracetamol was not present in patient sera and therefore we were studying the supportive effects of antagomir 324 in the context of patient recovery. The inhibition of miR-324-5p, by antagomir 324, resulted increased cell viability and caspase activity in 2 patients (Figure 6) suggesting a potential switch from cell necrosis to apoptosis. Contrary to these two patients, antagomir 324 did not have any rescue effect after exposure to the third patient’s serum. The exact reason for this is unknown, however, this patient possessed the lowest concentration of ALT which may have reflected a lesser liver injury and therefore lower toxic load to the cells (Supplementary Table 5).

In conclusion, we demonstrate that a novel miR inhibitor, antagomir 324, plays a major role in the regulation of SULT2A1, improving cell survival in the context of acute injury and patient recovery following paracetamol overdose. We believe that these studies are novel and offer serious promise to reduce the toxic effects of paracetamol overdose.
REFERENCES


FIGURE LEGENDS

Figure 1: Stagewise human embryonic stem cell (hESC) differentiation to the hepatocyte lineage. (A) Phase-constrast imaging demonstrated that cells underwent sequential morphological changes during transit from stem cell (day 0), to definitive endoderm (day 3), to hepatoblast (day 10), to hepatocyte (day 18). (B) Immunocytochemistry demonstrating upregulation of HNF4a and albumin during hepatic specification at day 18. Negative controls performed with corresponding immunoglobulin G (IgG). The percentage of positive cells is provided in the top right of each panel. This was calculated from four random fields of view and is quoted as ± standard error. (C) Cyp3A and Cyp1A2 metabolism were measured in day 18 hepatocyte like cells using the Promega pGlo system™. Experiments were performed in triplicate and measured on a luminometer. The units of activity quoted are relative light units per millilitre of supernatant per milligram of protein (RLU/mg/ml). The scale for all images represent 100 um. Abbreviations: HNF4a, hepatocyte nuclear factor 4a; ALB, Albumin.

Figure 2: Stem cell–derived (day 18) and primary human hepatocyte gene expression. The scatter plots represent expression of the major metabolic genes involved in Phase I, Phase II, and Phase III drug metabolism. Gene expression was performed using Human Drug Metabolism RT² Profiler PCR Array (QIAGEN) according to the manufacture’s instructions. The gene expression was analysed by RT2 Profiler PCR Array Data Analysis version 5.0 (QIAGEN). The scatter plot represents 3 fold change in gene expression. The graph plots the log₁₀ of normalized gene expression levels in a control condition, primary human hepatocytes (x-axis) versus an experimental condition, hESC-derived hepatocytes (y-axis). Symbols outside the boundary area indicate fold –differences larger than a threshold (3 fold). The red symbols in the upper - left corner readily identify up-regulated genes, and the green symbols in the lower-right corner readily identify down-regulated genes. The human primary hepatocyte total RNA was purchased from 3H Biomedical (Sweden).

Figure 3: The expression of enzymes and transporters involved in paracetamol (APAP) metabolism. (A) The panel represents protein expression of phase II enzymes GSTT1, SULT2A1 and Phase III transporters ABCC1, ABCG2 in stem cell – derived hepatocytes. The percentage of positive cells is provided in the top right of each panel. This was calculated from four random fields of view and is quoted as ± standard error. The images were taken at x 20 magnification. Scale bar represents 100 um. (B) Phase II enzymes (GSTT1, SULT2A1) and Phase III transporters (ABCG2, ABCC1) play major role in a toxic and non-toxic
pathways of paracetamol metabolism. In the non-toxic pathway paracetamol is metabolised by SULT2A1 enzymes to produce APAP sulfate metabolite that is effluxed from the cell by ABCG2 transporter. In a toxic pathway, paracetamol is metabolised by GSTT1 enzyme to produce APAP cysteine (mercapturic acid) metabolite that is effluxed from the cell by ABCC1 transporter. Abbreviations: GSTT1, glutathione-S-transferase theta 1; SULT2A1, sulfotransferase 2A1; ABCG2, ATP-Binding Cassette Transporter Subfamily G member 2; ABCC1, ATP-Binding Cassette Transporter Subfamily C member 1.

Figure 4: hESC-derived hepatocytes (hESC-heps) and primary human hepatocytes (PHH) microRNA expression profile. (A) Principle Component Analysis overview plot demonstrates strong clustering by cell type. (B) Statistical analysis of the microRNA Array demonstrates 367-reliably detected microRNAs in both hESC-heps and PHH; 220 microRNAs have a similar expression in both systems, and 147 microRNAs are differentially-expressed. (C) microRNA 122 (miR-122) is expressed in hESC-heps at the same level as in PHH. The microRNA Array was carried out by Sistemic Limited. The RNA samples (4 replicates of PHH and 4 experimental samples of hESC-derived hepatocytes) were run on Agilent miRNA platform.

Figure 5: Antagomir of microRNA 324 upregulated SULT2A1 gene and protein expression and increased cell survival after exposure to paracetamol. At day 17, hESC-heps were transfected with the antagomir of the corresponding microRNA at 50 nM for 24 hours. Transfection with the Ant-324-5p upregulated SULT2A1 gene expression by 2-fold (A) and protein expression by 20% (B) in comparison with the scrambled control. At day 17, hESC-hepatocytes were either transfected with antagomirs or treated with 1 mM N-acetylcysteine (NAC) concentration for 24 hours. At day 18, the the antagomir transfected or NAC pre-exposed hESC-hepatocytes were exposed to paracetamol concentration that causes 50% of the cell death (IC50 = 12.85 mM) for another 24 hours. At day 19, the cell viability was measured using CellTitre Assay (Promega) and Glutathione Depletion Assay (Promega). The antagomir of microRNA 324 (Ant 324) significantly increased ATP to the levels comparable with NAC (fold increase was calculated in comparison with control; the values for Ant ctrl = 2.17 x 10^6; Ant 324 = 3.12 x 10^8; H2O (vehicle) = 2.38 x 10^6; NAC = 3.86 x 10^8 (C) and enhanced reduced glutathione levels (D). Levels of significance were measured by Student’s t test. Significance levels are denoted by one asterisks to indicate p < 0.05. The percentage of positive cells is provided in the top right of each panel. This was calculated from four random fields of view and is quoted as ± standard error. The scale bar represents: 100 um.
Abbreviations: SULT2A1, sulfotransferase 2A1; Ant Control; Scrambled Antagomir Control; Ant 324; Antagomir 324-5p. Levels of significance were measured by Student’s t test. Significance levels are denoted by one asterisk to indicate p < 0.05.

**Figure 6:** hESC-derived hepatocytes transfected with the antagomir to miR-324-5p. Twenty four hours post transfection hESC-hepatocytes were exposed to the plasma from patients with fulminant hepatic failure for a further twenty four hours (Patients 1, 8 and 58). ATP levels and caspase 3/7 activation were determined using Promega Glo technology and measured on a luminometer (Promega). Units of activity are expressed as relative light units (RLU) ml⁻¹ (n=4). Levels of significance are quoted and measured by Student’s t-test. Significance levels are denoted by one and two asterisks to indicate p < 0.05 and p < 0.01 respectively.

**Supplementary Figure 1:** Metabolic activity of female and male primary human hepatocytes. Cyp3A and Cyp1A2 metabolism were measured in both lines 48 hours post-replating using the Promega pGlo system™. Experiments were performed in triplicate and measured on a luminometer. The units of activity quoted are relative light units per millilitre of supernatant per milligram of protein (RLU/mg/ml).

**Supplementary Figure 2:** Paracetamol (APAP) metabolism (based on Pharmacogenomics Knowledge Base PharmGKB; [www.pharmgkb.org](http://www.pharmgkb.org)). At normal doses APAP is metabolised by two major families of phase II enzymes: Sulfotransferases (SULTs) and UDP-glucuronosyltransferases (UGTs). This leads to the production of two metabolites: APAP-sulfate and APAP-glucuronide, which are further effluxed from the cell by one of the ABC transporters. At higher doses than recommended, paracetamol is metabolised by Cytochrome P450 enzymes. This leads to the formation of a reactive metabolite, N-acetyl-p-benzoquinoneimine (NAPQI), which is further transformed to a non-toxic APAP-cysteine by Glutathione –S- transferases (GSTT1,GSTP1). The metabolite is effluxed from the cell by one of the phase III transporters.

**Supplementary Figure 3:** Paracetamol in vitro toxicity in stem-cell derived hepatocytes (hESC-heps) and primary human hepatocytes (PHH). hESC-heps (at day 17) and PHH (24 hours post-replating) were induced with different concentrations of paracetamol (0-50 mM) for 24 hours. The CellTitre viability assay (Promega) was used to measure the ATP levels. The IC50 was calculated from the function f(x)= ax + b.
**Supplementary Figure 4:** At day 17, hESC-heps were transfected with the antagomir of the corresponding microRNA at 50 nM concentration for 24 hours. Transfection with the antagomir of microRNA 24-3p did not have any effect either on gene (A) or protein (B) expression of GSTT1. At day 18, the transfected hESC-heps were exposed to paracetamol concentration that causes 50% of the cell death (IC50 = 12.85 mM) for another 24 hours. At day 19, the cell viability was measured using CellTitre Assay (Promega) and Glutathione Depletion Assay (Promega). The Ant-24 decreased cell viability (C) and reduced glutathione (D) after exposure to paracetamol comparing to the scrambled control. The percentage of positive cells is provided in the top right of each panel. This was calculated from four random fields of view and is quoted as ± standard error. The scale bar represents: 100 um. Abbreviations: Ant Control; Scrambled Antagomir Control; Ant 324; Antagomir 324-5p.

**Supplementary Figure 5:** At day 17, hESC-derived hepatocytes were transfected with precursors at 50nM concentration for 24 hours. At day 18, cells were exposed to paracetamol (APAP) concentration that causes 50% of the cell death (IC50 = 12.85 mM) for 24 hours. At day 19, the cell viability and glutathione reduction were measured using CellTiter – Glo® Luminescent Cell Viability Assay (Promega) and GSH/GSSG – Glo™ Assay (Promega) respectively. Abbreviations: Pre; precursor. Pre ctrl/Pre 24/Pre 324, precursor scrambled control/ precursor of miR -24/ precursor of miR -324-5p. Levels of significance are quoted and measured by Student’s *t*-test. Significance levels are denoted by one asterisks to indicate p < 0.05.

**Supplementary Table 1:** Fold-Change ($2^{\Delta \Delta Ct}$) is the normalized gene expression ($2^{\Delta Ct}$) in the Test Sample divided the normalized gene expression ($2^{\Delta Ct}$) in the Control Sample. Fold-Regulation represents fold-change results in a biologically meaningful way. Fold-change values greater than one indicate a positive- or an up-regulation, and the fold-regulation is equal to the fold-change. Fold-change values less than one indicate a negative or down-regulation, and the fold-regulation is the negative inverse of the fold-change. Up-regulated genes (fold differences larger than a 3 fold threshold) are indicated in red, down-regulated genes (fold differences narrower than 3 fold treshold) are indicated in green. Genes similarly expressed for the Group 1 and Control (fold differences between -3 to +3 boundary) are indicated in black. Abbreviations: HLC, hepatocyte-like-cells; PHH, primary human hepatocytes.
**Supplementary Table 2:** The list of 220 microRNAs commonly expressed in stem cell–derived hepatocytes (day 18) and primary human hepatocytes (PHH). The RNA samples (4 replicates of PHH and 4 experimental samples of hESC-derived hepatocytes) were analysed on the Agilent miRNA platform (using Agilent’s SurePrint G3 Human v16 microRNA 8x60K microarray slides; miRBase version 16.0.

**Supplementary Table 3:** Predicted microRNA/mRNA binding site by TargetScanHuman5.2 (www.targetscan.com). (A) Human microRNA hsa-miR-324-5p has been predicted to bind its target gene SULT2A1 at the 3’ untranslated region at position between 639-645 nt. Human microRNA has-miR-24-3p has been predicted to bind its target gene GSTT1 at the 3’ untranslated region at position between 266-272 nt. (B) The table represents type of seed match and context score for each of the microRNA/mRNA binding. (C) The table represents the miRBase accession number of each of the selected microRNAs and UniGene and GeneBank of selected genes of interest. Abbreviations: SULT2A1, sulfotransferase 2A1; GSTT1, glutathione-s-transferase theta 1.

**Supplementary Table 4:** The table demonstrates qPCR primers, and primary/secondary antibodies used in this study.

**Supplementary Table 5:** Anonymised patient details. (A) The table represents the plasma contents of each of the patients used in this study. (B) The table represents normal ranges for particular sera and international normalized ratio (INR). ALT and BILI are liver function tests. Creatinine is a measure of renal function, which is often compromised in liver disease INR is International Normalized Ratio of the prothrombin time, a coagulation function test.
Figure 2

Phase I

Phase II

Phase III

Log 10 (Control Group; 2Λ – DeltaCt)

Log 10 (Control Group; 2Λ – DeltaCt)

Log 10 (Control Group; 2Λ – DeltaCt)

Incr

eas

Decr
ea

Simil
ar

Increased   Decreased   Similar
Figure 3

297x209mm (300 x 300 DPI)
### Primary Hepatocytes versus hESC-derived hepatocytes

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**Figure 4**
Figure 5

254x190mm (200 x 200 DPI)
Figure 6

254x190mm (96 x 96 DPI)
Supplementary Figure 1

**CYP3A**

**CYP1A2**
APAP metabolic pathway

NAPQI

APAP-cysteine

CYP2E1
CYP3A4
CYP1A2
CYP2D6

GSTT1
GSTP1
ABCC1
ABCC4
ABCC5

Efflux

APAP-sulfate

SULT2A1
SULT1A1
SULT1A4
SULT1A3
UGT1A1
UGT1A6
UGT1A9
UGT2B15

Phase I
Phase II
Phase III

APAP-glucuronide

UGT1A6
UGT1A9
UGT2B15

ABC2G
ABCB1

Efflux

hepatotoxicity

Phase I
Phase II
Phase III

Supplementary Figure 2
Supplementary Figure 4
Supplementary Figure 5

254x190mm (96 x 96 DPI)
### Supplementary Table 1

**RT² PROFILER PCR ARRAY - Human Drug Metabolism Phase I (QIAGEN; PAHS-002Z)**

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**RT² PROFILER PCR ARRAY - Human Drug Metabolism Phase II (QIAGEN; PAHS-069Z)**

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### RT² PROFILER PCR ARRAY - Human Drug Transporters Phase III (QIAGEN; PAHS-0702)

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## Supplementary Table 3

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<th>mRNA/microRNA</th>
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Position 639-645 of SULT2A1 3' UTR

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<th>hsa-miR-324-5p</th>
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<td>3' UGUGGUUACGGGAUCCCCUACGC</td>
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Position 266-272 of GSTT1 3' UTR

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### B)

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<th>Context + score percentile</th>
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### C)

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<td>Abcam</td>
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<td>Rabbit polyclonal</td>
<td>1:500</td>
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<td>Mouse monoclonal</td>
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Supplementary Table 5

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<th>BILIRUBIN (umol/L)</th>
<th>INR RATIO (ratio)</th>
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B)  

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Graphical abstract
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